

# IMMUNITY

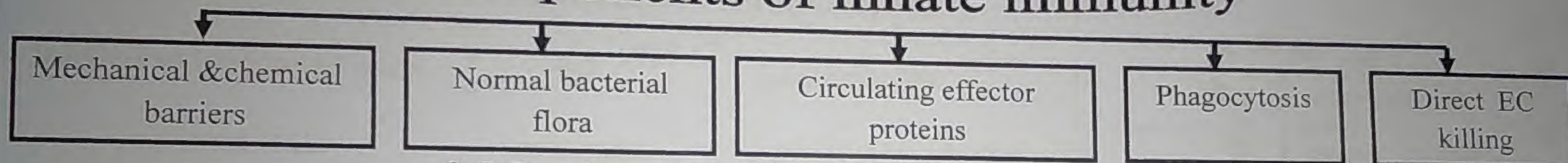
**Innate (natural) immunity**

1<sup>st</sup> line of defense

**Acquired (Adaptive) immunity**

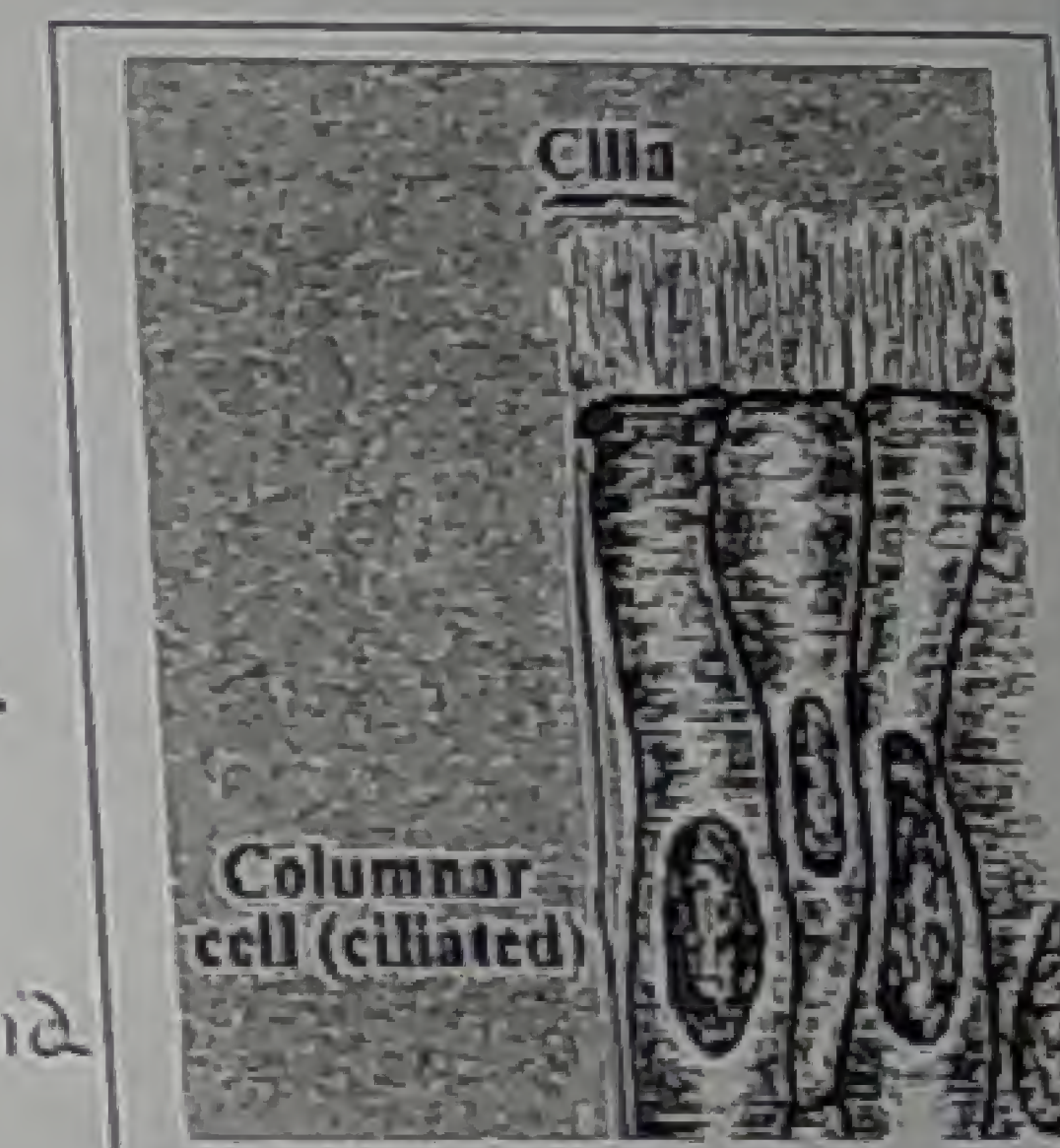
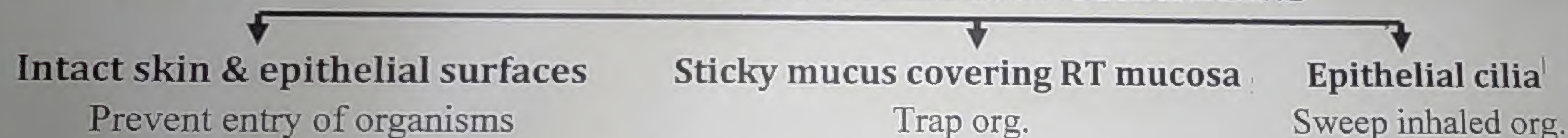
2<sup>nd</sup> line of defense : B & T lymphocytes

## Components of innate immunity



## I-Mechanical & Chemical barriers

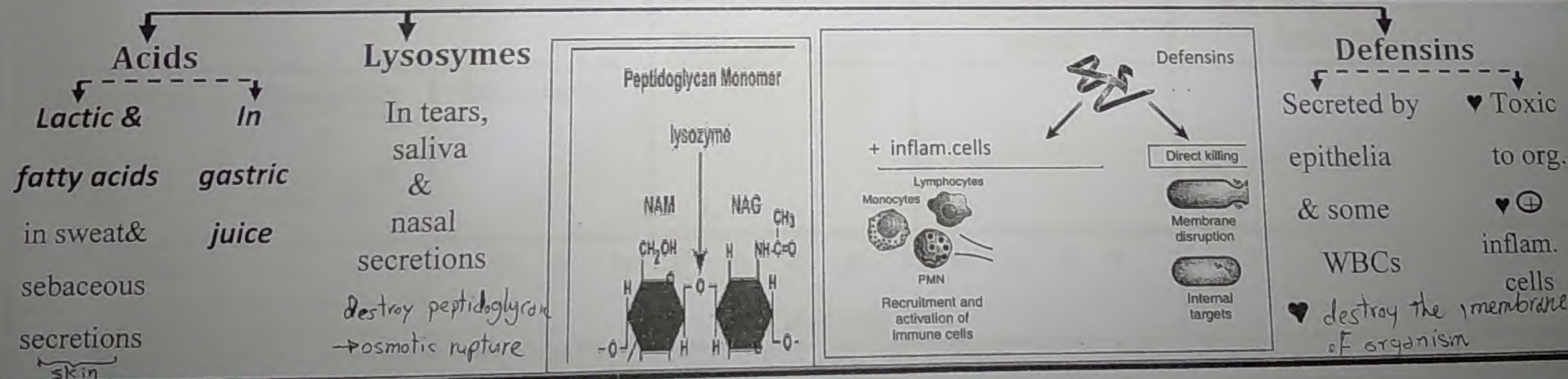
### A-Mechanical barriers



### B-Chemical barriers

Microbicidal factors in BF<sub>s</sub>

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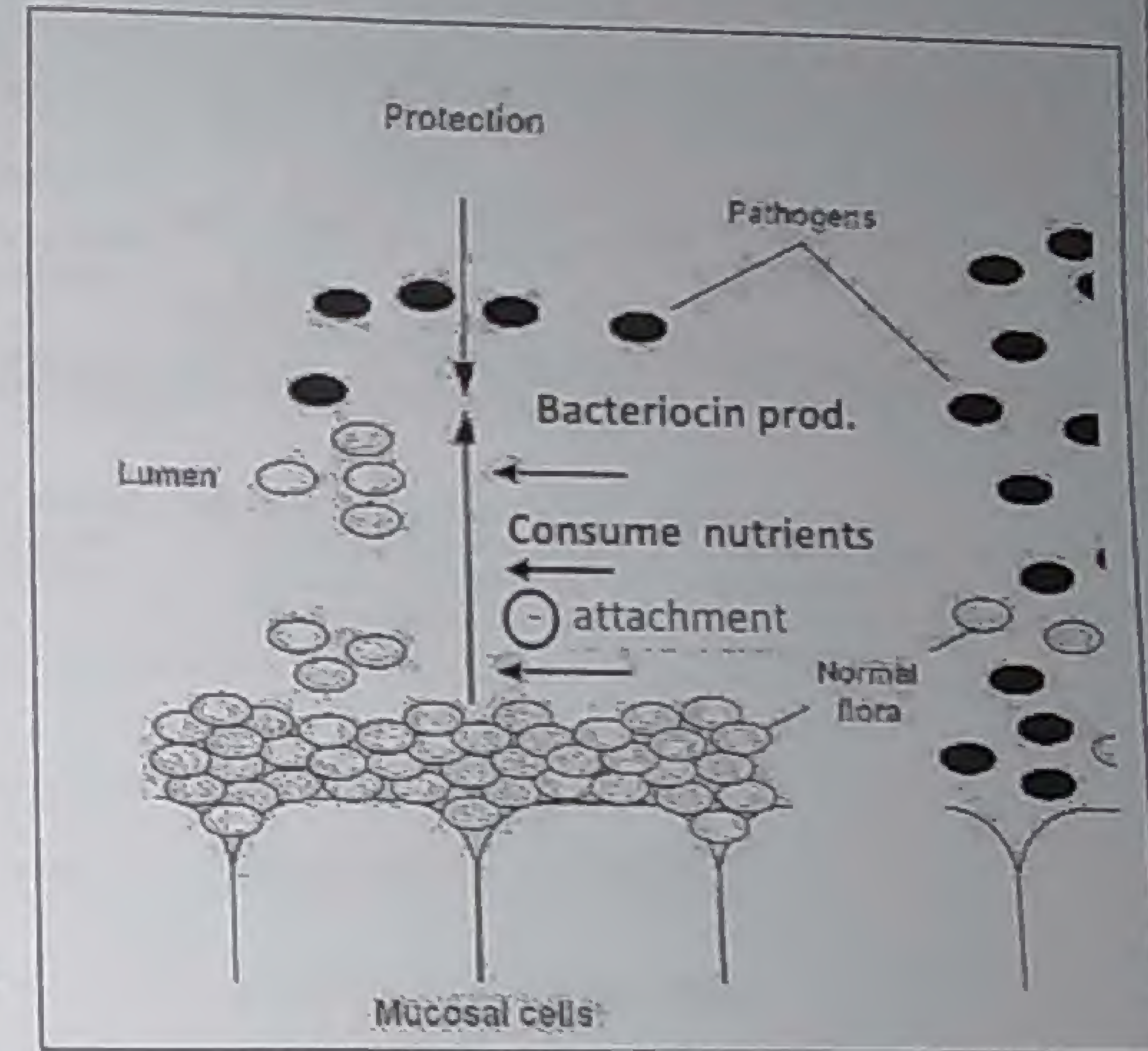
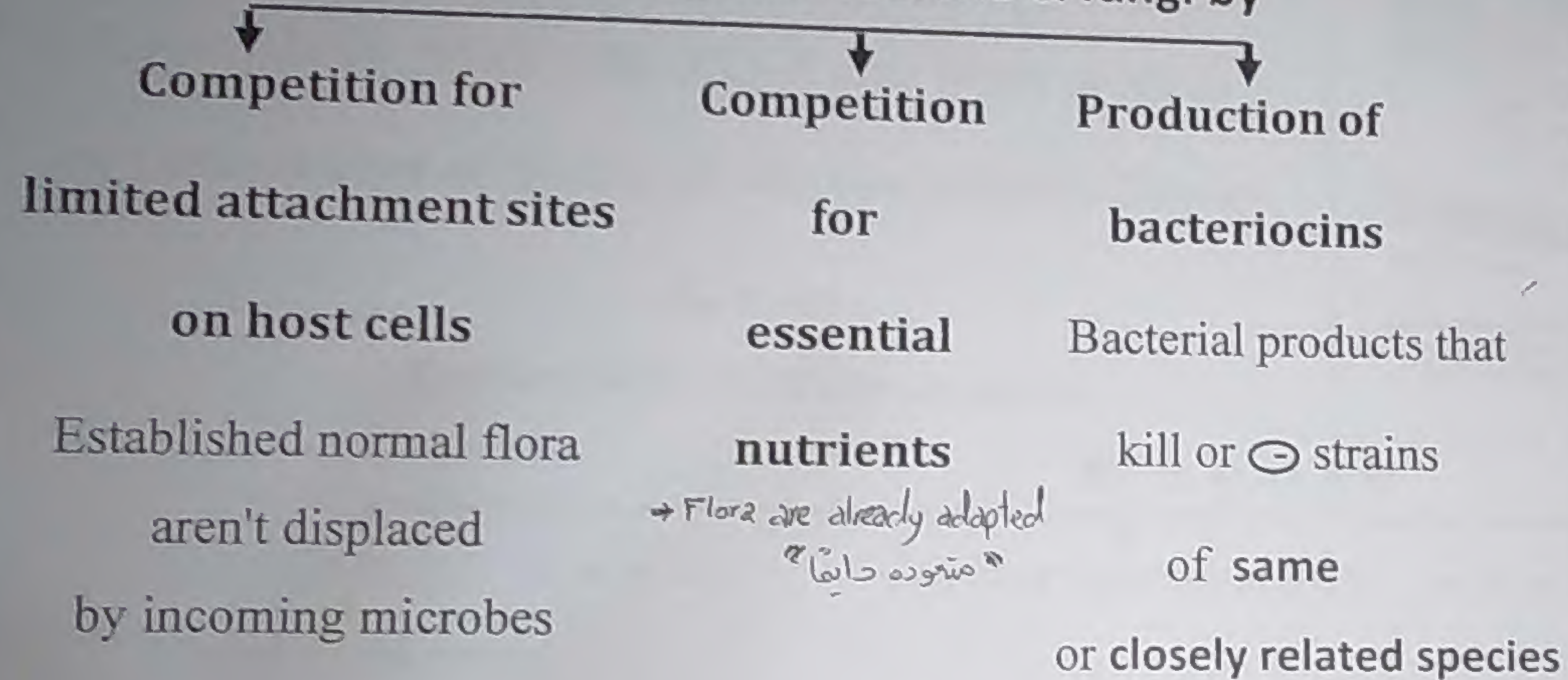




## II - Normal bacterial flora

تدخل - من النفس والكل والكبر

⊖ growth of pathogenic bacteria & fungi by



## Cells of innate immunity

Granulocytes		Monocytes & Macrophages	Dendritic cells	Natural killer cells (non-phagocytic cells) — (lymphocytes)
Eosinophils	Basophils & Mast cells	Neutrophils		
EC killing		P h a g o c y t o s i s (IC Killing)		EC killing (cytotoxicity) 2
Inflammation in mucosa				

non-professional



# Inflammation

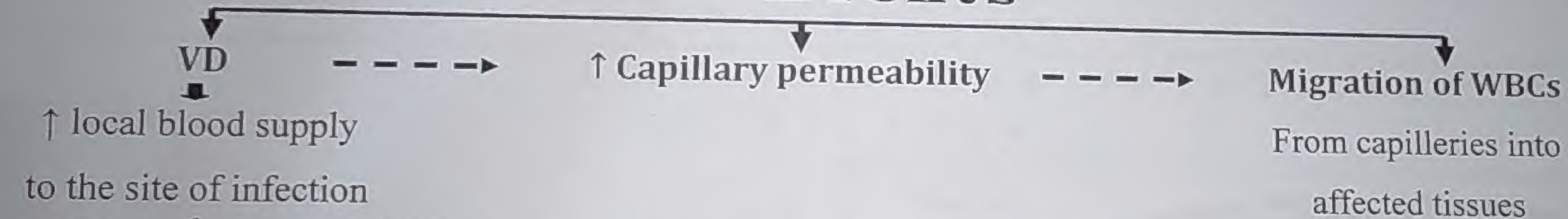
## Definition

Process during which cells of IS & their active products are concentrated at the site of infection or tissue damage

## Aim

Eradication of infectious agents

## Events



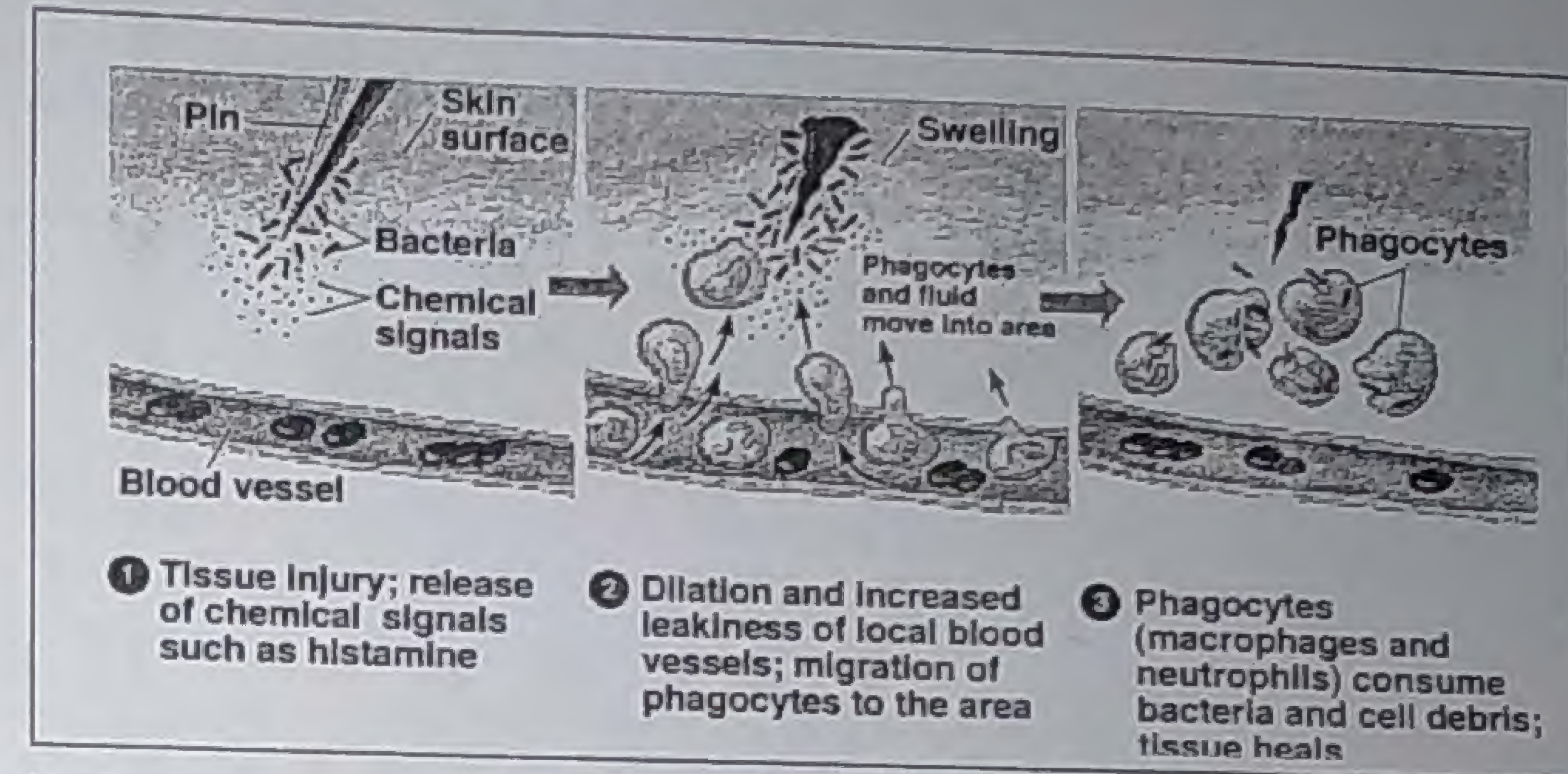
## Harmful effects

**Mechanical obstruction of airways**

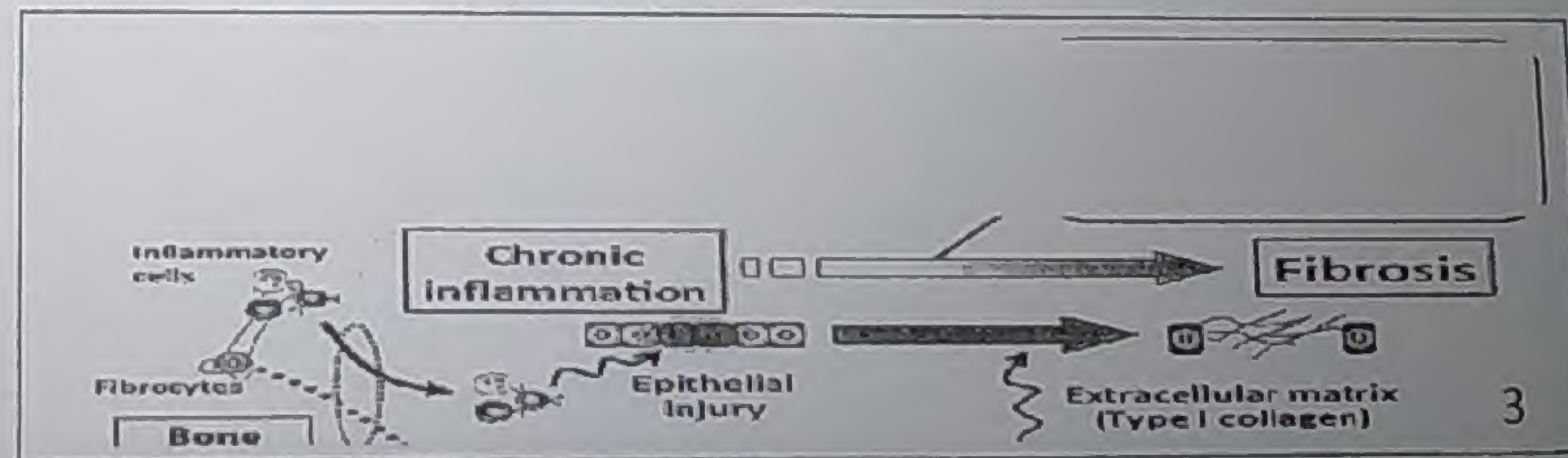
By swollen epiglottis → acute epiglottitis

**Scarring & Loss of functions**

By tissue damage due to chronic inflam.

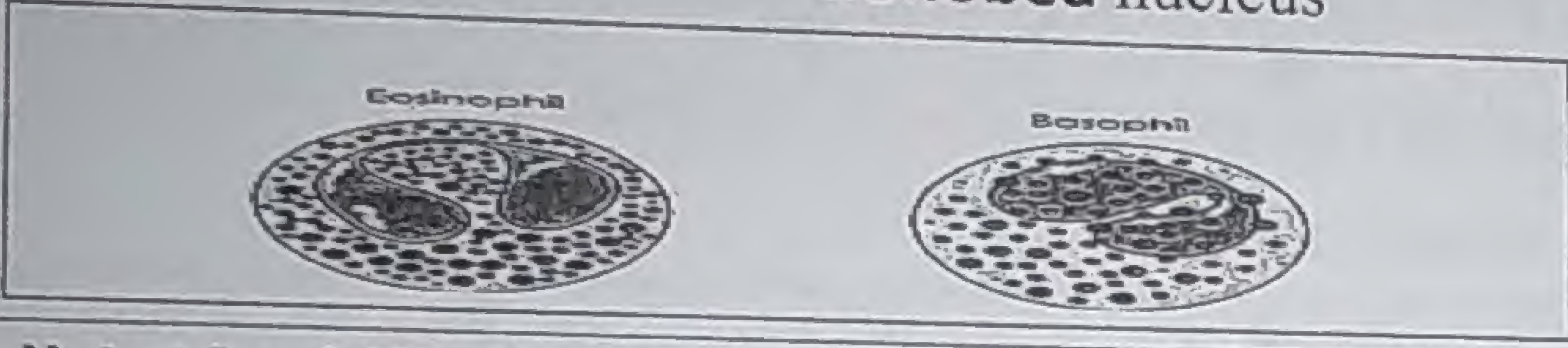
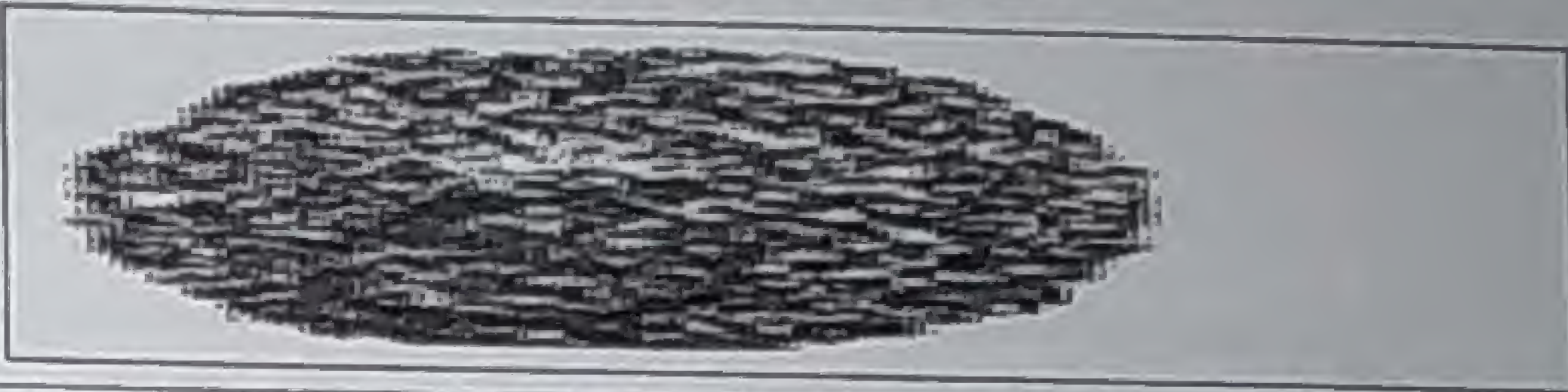

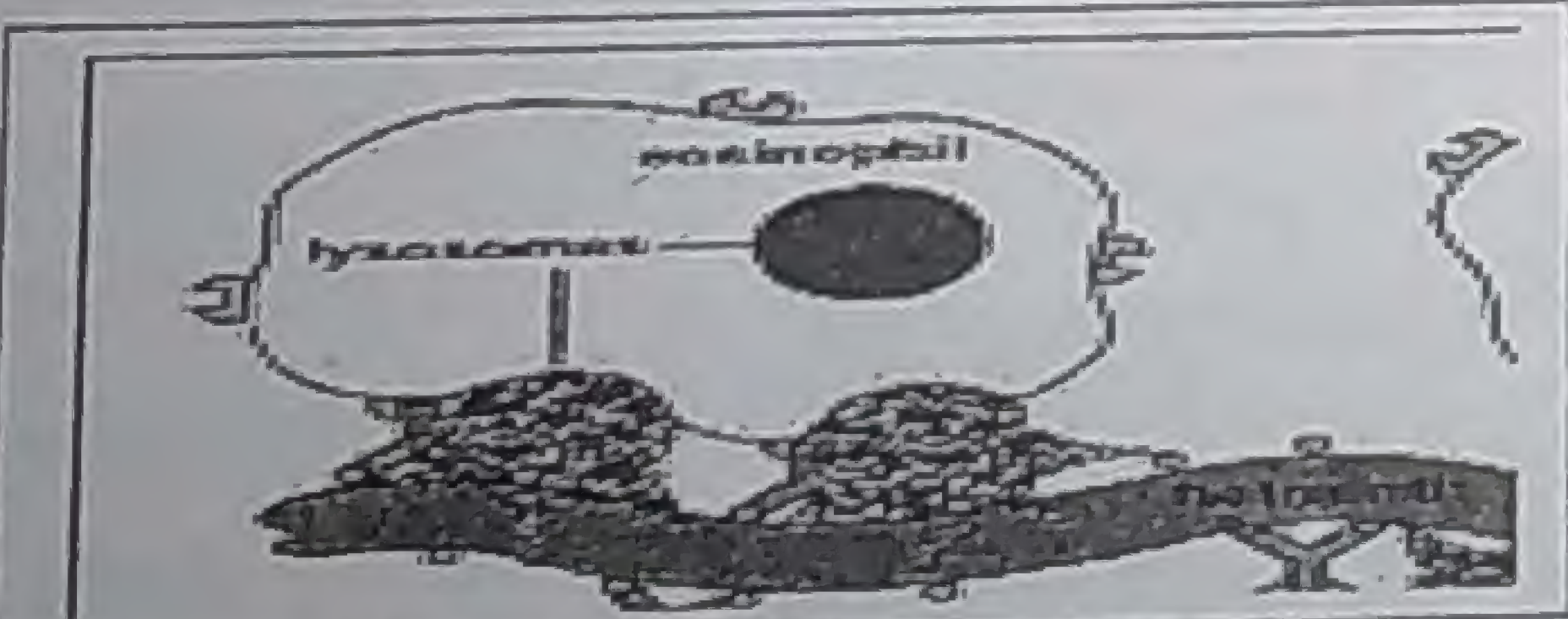


Narrow airway





# Important inflammatory cells

Important inflammatory cells			
1-Site	Eosinophils	Basophils	Mast cells
2-Structure	Blood → recruited out to tissues (when needed)		Fixed in tissues :under skin,mucosa of RT&GIT
	i.Bilobed nucleus		i.Round nucleus
			
	ii.Acidophilic granules containing: ♪ Basic protein	ii. Basophilic granules containing: ♪ Histamine	
3-Functions	♪ Peroxidase ♪ Hydrolase		
	i. Inflammation in mucosa ii. Allergy		
	<div><div>Mast cells or basophils</div><div>Histamine</div><div>Allergic Response</div></div>		
	iii. Damaging parasites		

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### III - Circulating effector proteins

### A - Complement System

Group of soluble plasma proteins (C1-C9) circulating in inactive form

**Activated** (in cascade manner) *by microbial surfaces (Ags)*

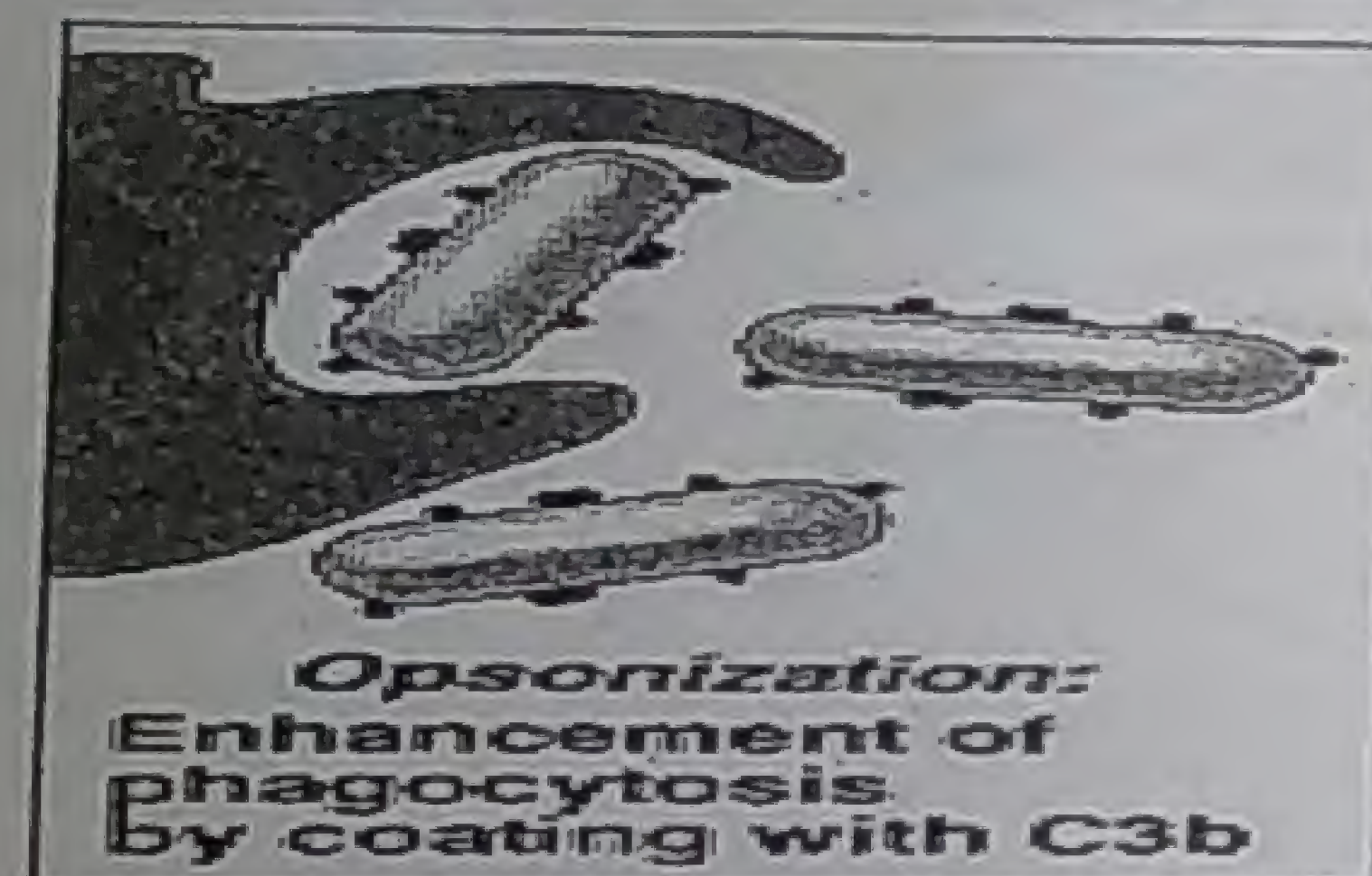
## Functions

**Direct lysis**  
of bacteria  
(C5b6789)

Enhance phagocytosis  
(C3b is opsonin)

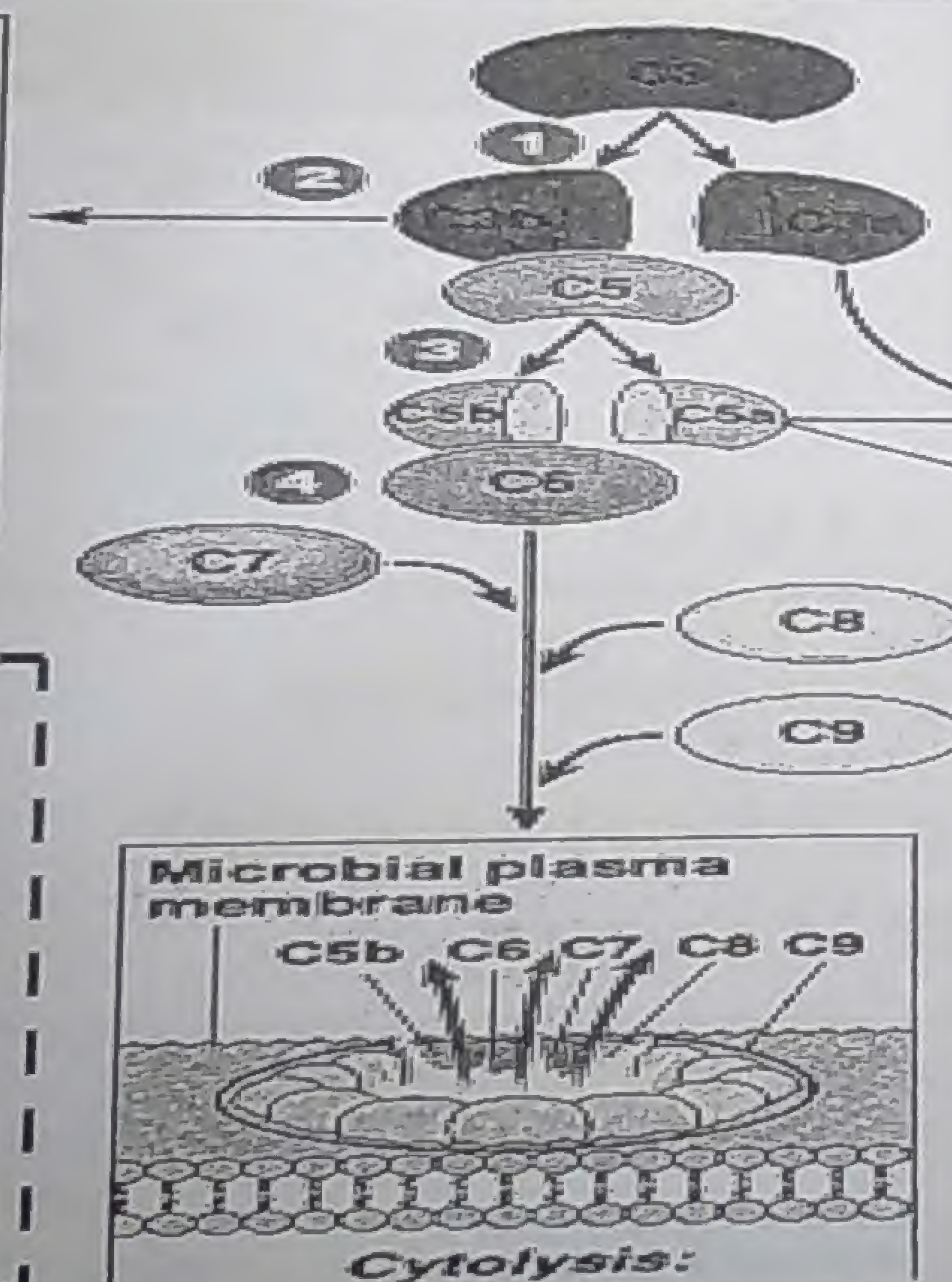
Degranulation of mast cells & basophils (C3a & C5a)  
 ↓  
 ↑ vascular permeability & recruitment of phag. cells

**Chemotaxis**  
Phagocytes  
(C5a)



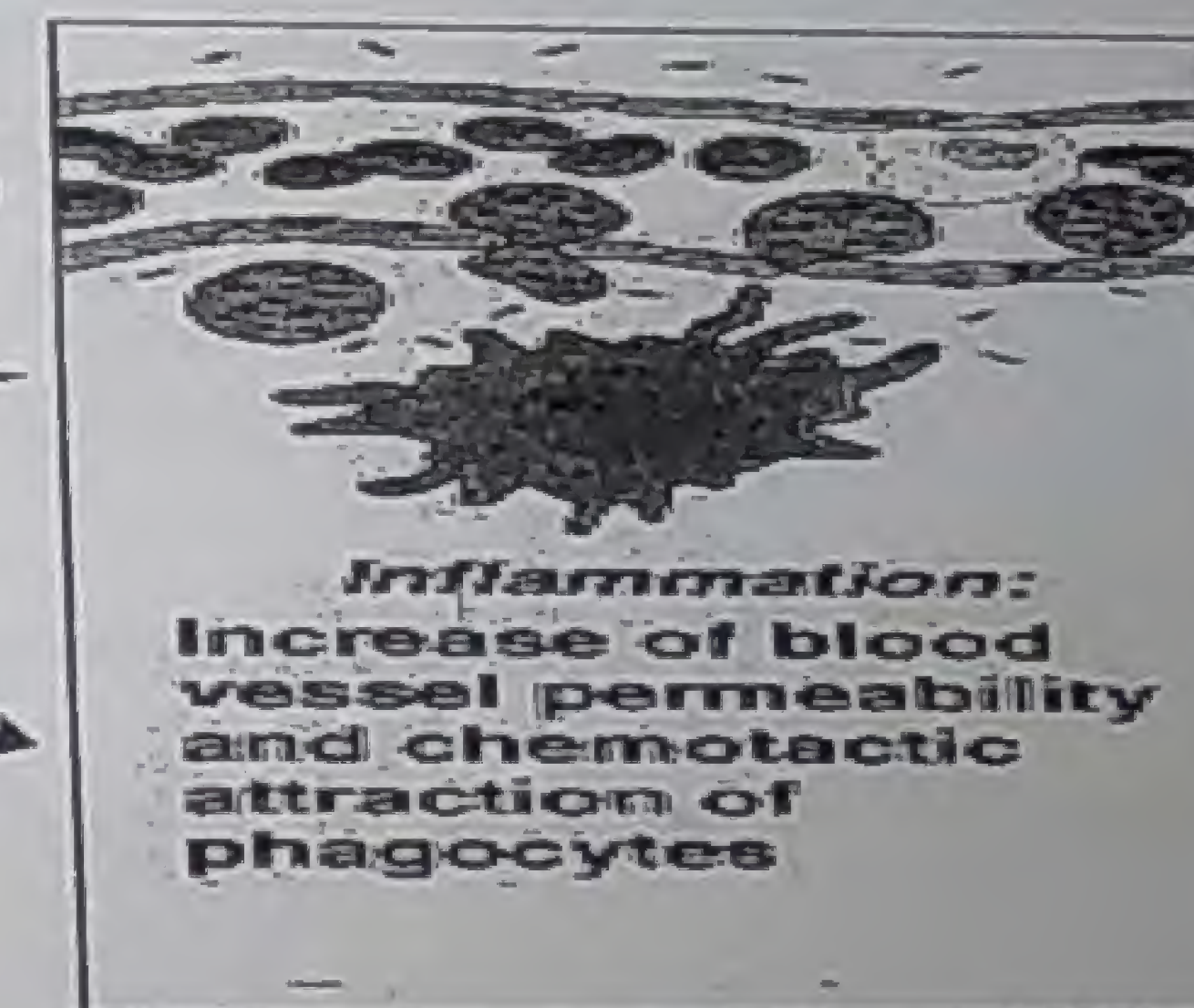
## Opsonization

A process in which an org. is rendered more susceptible to phagocytosis by coating an opsonin (blood serum protein) e.g C3b, Ab, acute phase protein



### Direct bacterial lysis

### Degranulation & Chemotaxis





## B-Acute phase proteins

Release  
From liver

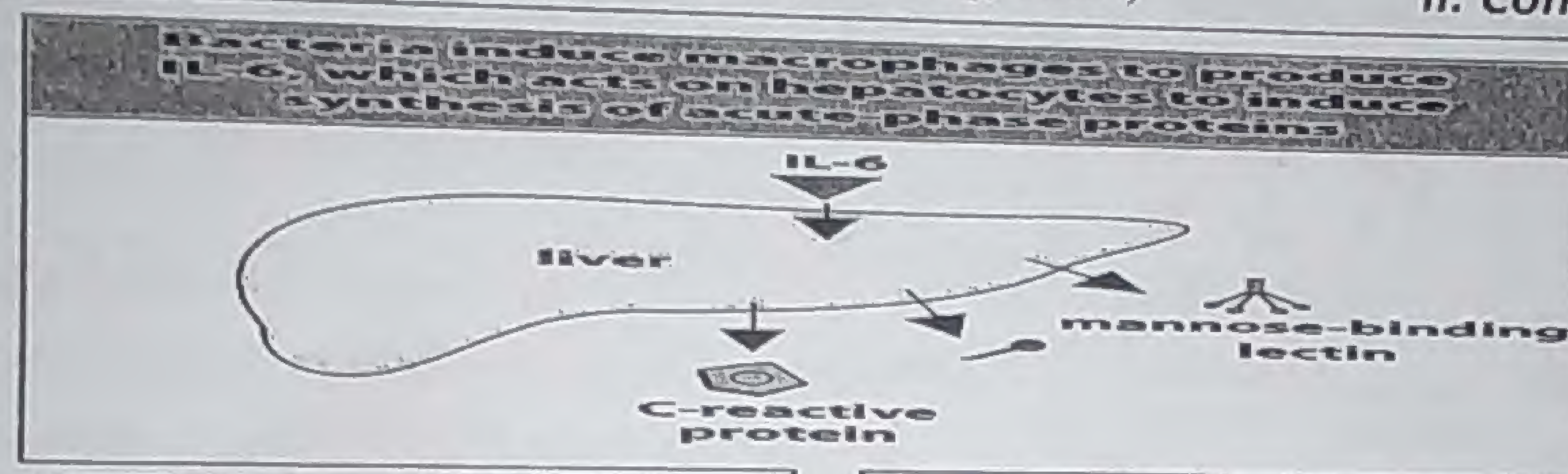
Examples

- C-reactive protein
- Mannose binding protein (lectin)

Functions

- i. Enhance phagocytosis (opsonins)
- ii. Complement activation

under effect of  $TNF\alpha, IL1\&6$



C-reactive protein binds to bacterial surfaces, acting as an opsonin and as a complement activator



Mannose-binding lectin binds to bacterial surfaces, acting as an opsonin and as a complement activator



## C-Cytokines

Low MW & soluble proteins

Produced in response to injury by microbes

Allow cellular communications

### Cytokines regulating innate immunity

Produced mainly by *MQ & dendritic cells*

6

Inflammatory cytokines	Interferons	IL10
✓ $TNF\alpha, IL1, IL6$ & Chemokines e.g $IL8$	✓ $IL12$	✓ $IL18$
	Antivirals	Inhibitory



# Inflammatory Cytokines

Produced mainly from MQ and DCs (on recognizing microbes by PAMP receptors)

1-TNF $\alpha$ (Cachectin)	2-IL1	<div> <div>Local inflammation</div> </div> <div> <div>Systemic protective effects</div> </div> <div> <div>Systemic pathological effects</div> </div>	
Sources			
i. MQ & dendritic cells			
ii. Th1	ii. Endothelial cells		
Functions			
i-Acute inflammatory (phase) response			
a. Endothelial cells: VD ( $\uparrow$ permeability) & activation of coagulation			
b. Recruitment of neutrophils to site of inf. & their activation			
c. Liver: synthesis of acute phase proteins			
d. Hypothalamus: fever (endogenous pyrogen)			
e. Muscle wasting & fat catabolism $\rightarrow$ Cachexia			
ii-Tumor necrosis	ii- $\oplus$ of adaptive immunity		
	a. $\oplus$ B cells		
	Proliferation & differentiation into plasma cells		
	b. $\oplus$ Th cells		
	3-IL6	4-Chemokines	
Sources	i. MQ, dendritic cells & endothelial cells		
	ii. Th2	ii. T cells, platelets & fibroblasts	
Functions	i. Acute inflammatory response: a, b & c (M)	Migration of neutrophils & lymphocytes from blood to site of infection	
	ii. $\oplus$ of adaptive immunity		
	$\odot$ B cells $\rightarrow$ Proliferation & differentiation into plasma cells		



# IV- Phagocytosis

## Phagocytic Cells

### Neutrophils

### Monocytes & MQ

### Dendritic cells

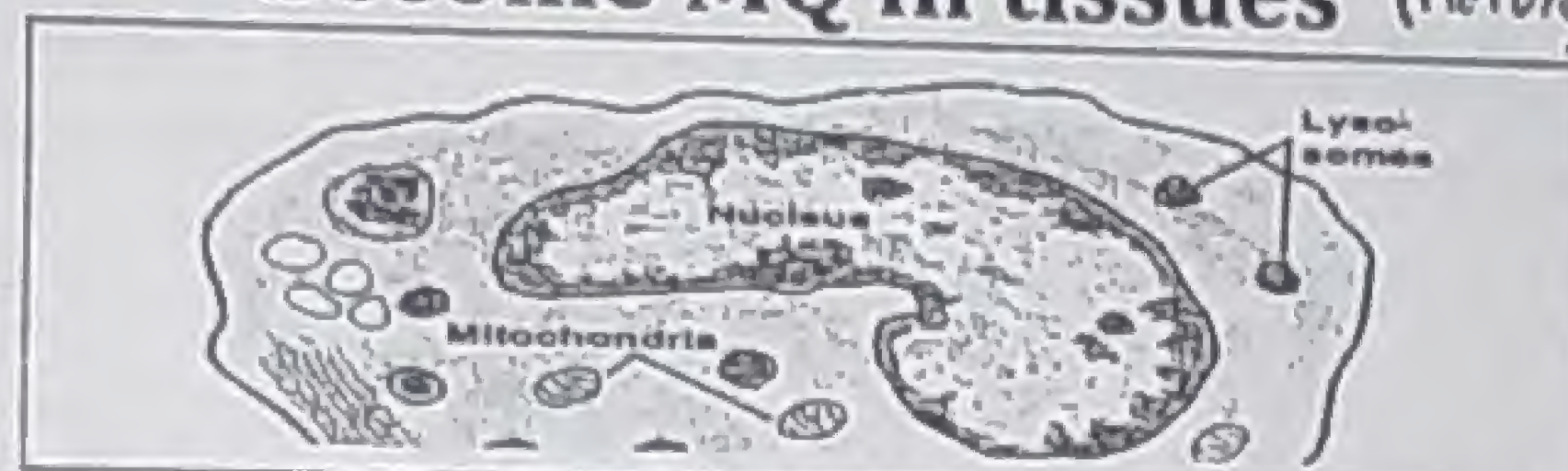
I- Origin : BM progenitor cells

II - Site

The most abundant WBCs in blood  
 1<sup>st</sup> phagocytic cell that encounter the infection  
 May migrate into tissue spaces  
 ↑ in n= in acute bacterial infections  
 Eosinophilia (not neutrophils) → indicates → ABL

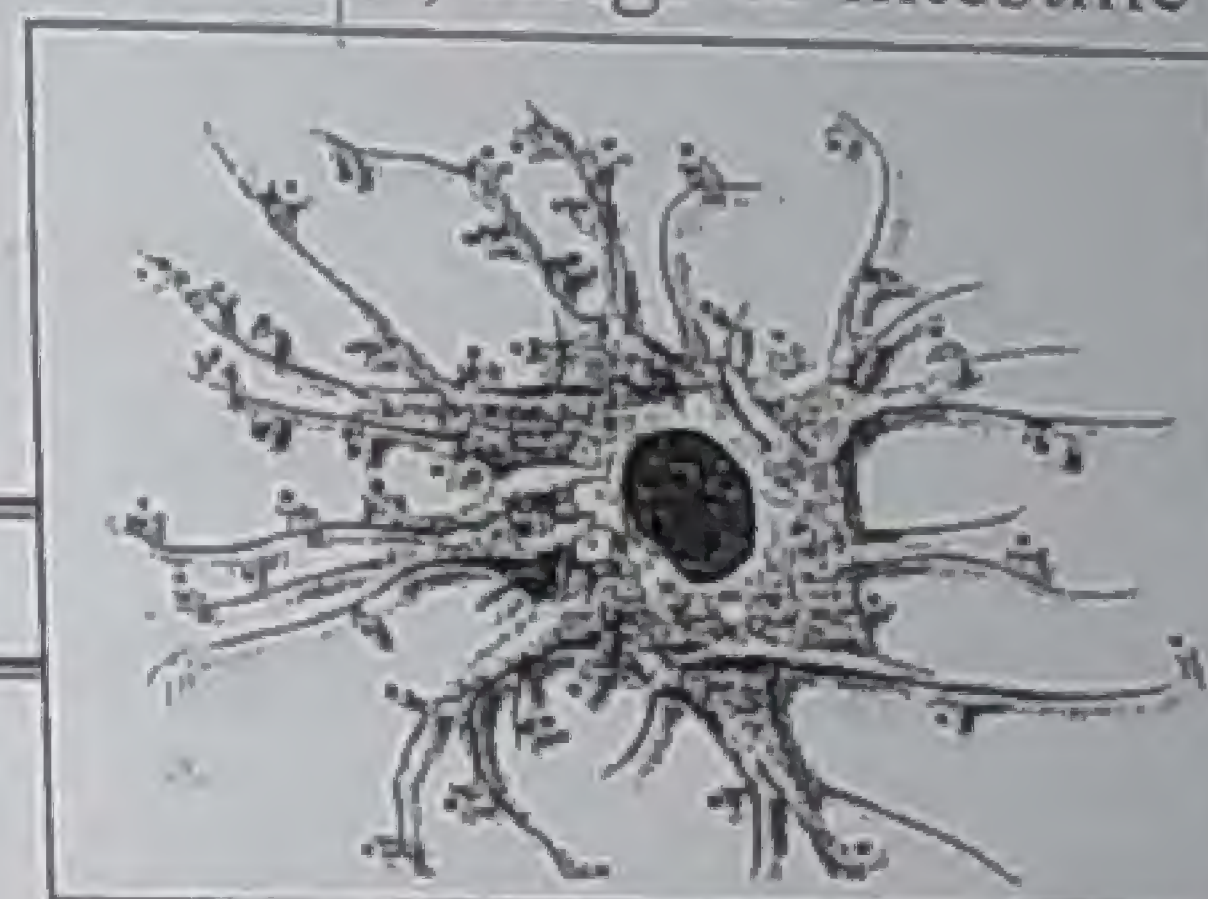
Monocytes circulate in blood

Become MQ in tissues (Mature)



♣ Skin

♣ MM of nose, lungs & intestine



III - Structure

♥ Segmented nucleus

♥ Cytoplasmic lysosomes filled with:

♥ Kidney shaped nucleus

♥ Cytoplasmic lysosomes filled w:

i-Lysosomes collagenase elastase

ii-Defensins (EC organism <sup>Most</sup> Bacteria)

Dendritic=branched like a tree  
 (From Greek "dendron")

IV - Functions

1 - Phagocytosis

Ingestion & killing of bacteria and viruses.  
 (Few TB)

NO

2-Professional APCs

→ Activate T cells

Antigen presenting  
 8 cells

Main APC : Migratory cell

Travel to LN&spleen to ⊕ T cell





# Response of phagocytic cells to infection

1-If an org. invades the mechanical and chemical barriers & the effect of normal flora

Encounter *resident MQ & dendritic cells* in subepithelial tissues

(When org. invades blood → encounters circulating neutrophils & monocytes).

## 2 - Recruitment of neutrophils from BVs to site of inf.

Resident MQ & Dendritic cells secrete **inflammatory cytokines** that   
 ↑ expression of adh. mol.   
 Cause VD & Chemotaxis

a. ↑ expression of adhesion molecules by  $TNF\alpha$ , IL1 & 6 on both

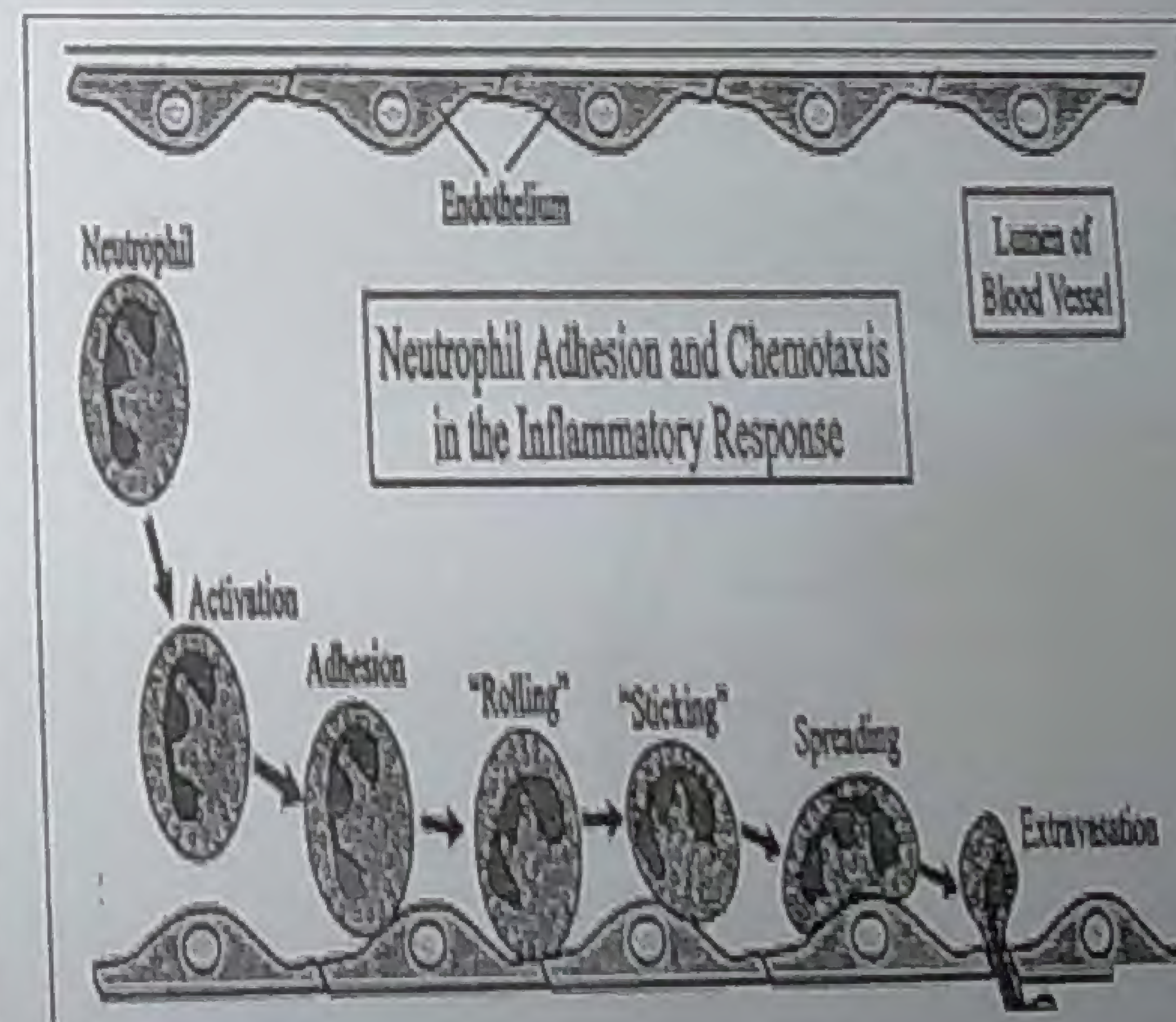
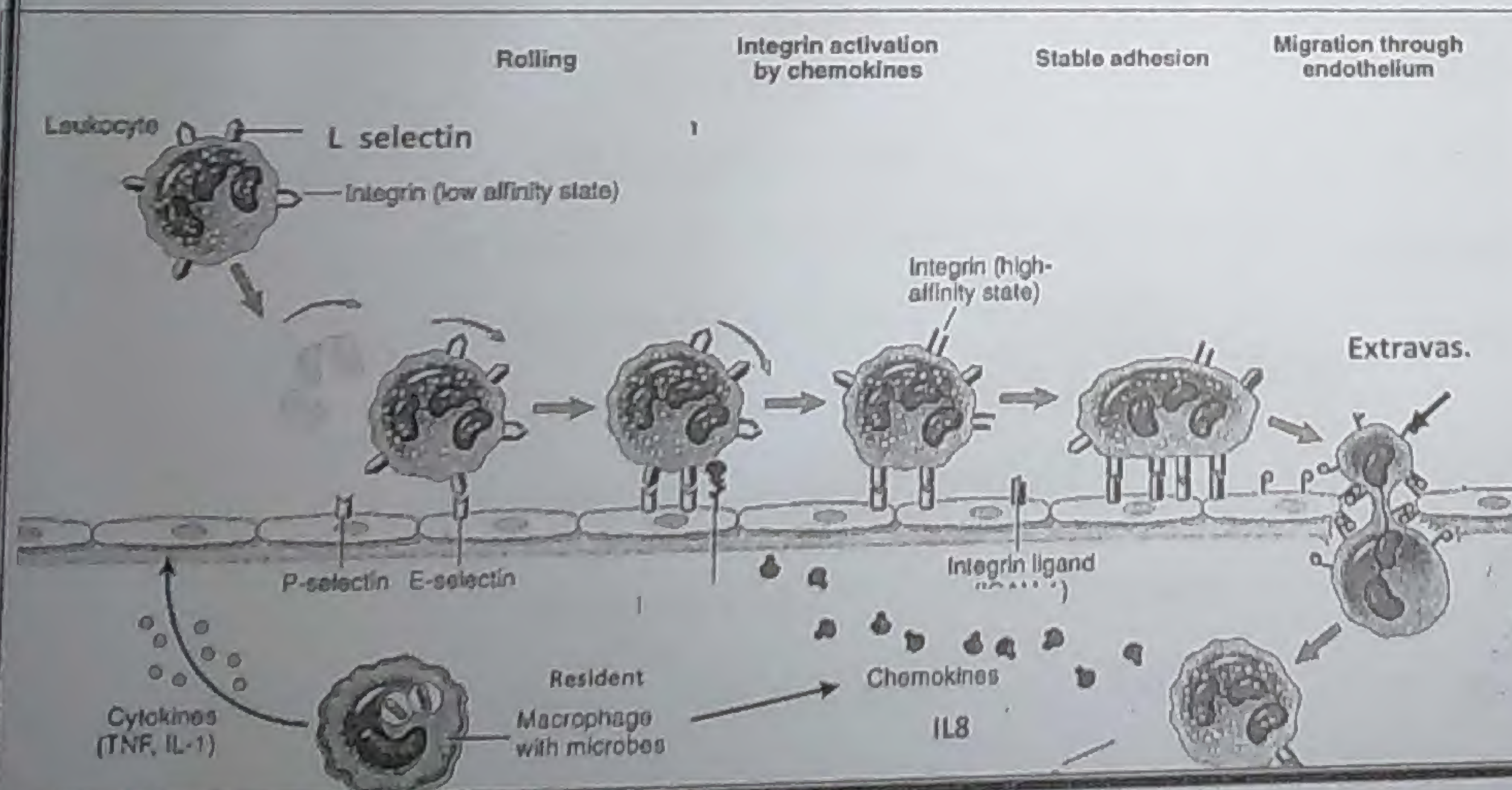
↓ **Endothelial cell surfaces**

♦ E&P selectin ♦ Integrin ligand

↓ **Leukocytes**

♣ L selectin ♣ Integrin

Neutrophils adhere to endothelium (**Adhesion**) → **Rolling** → **sticking** → **spread**





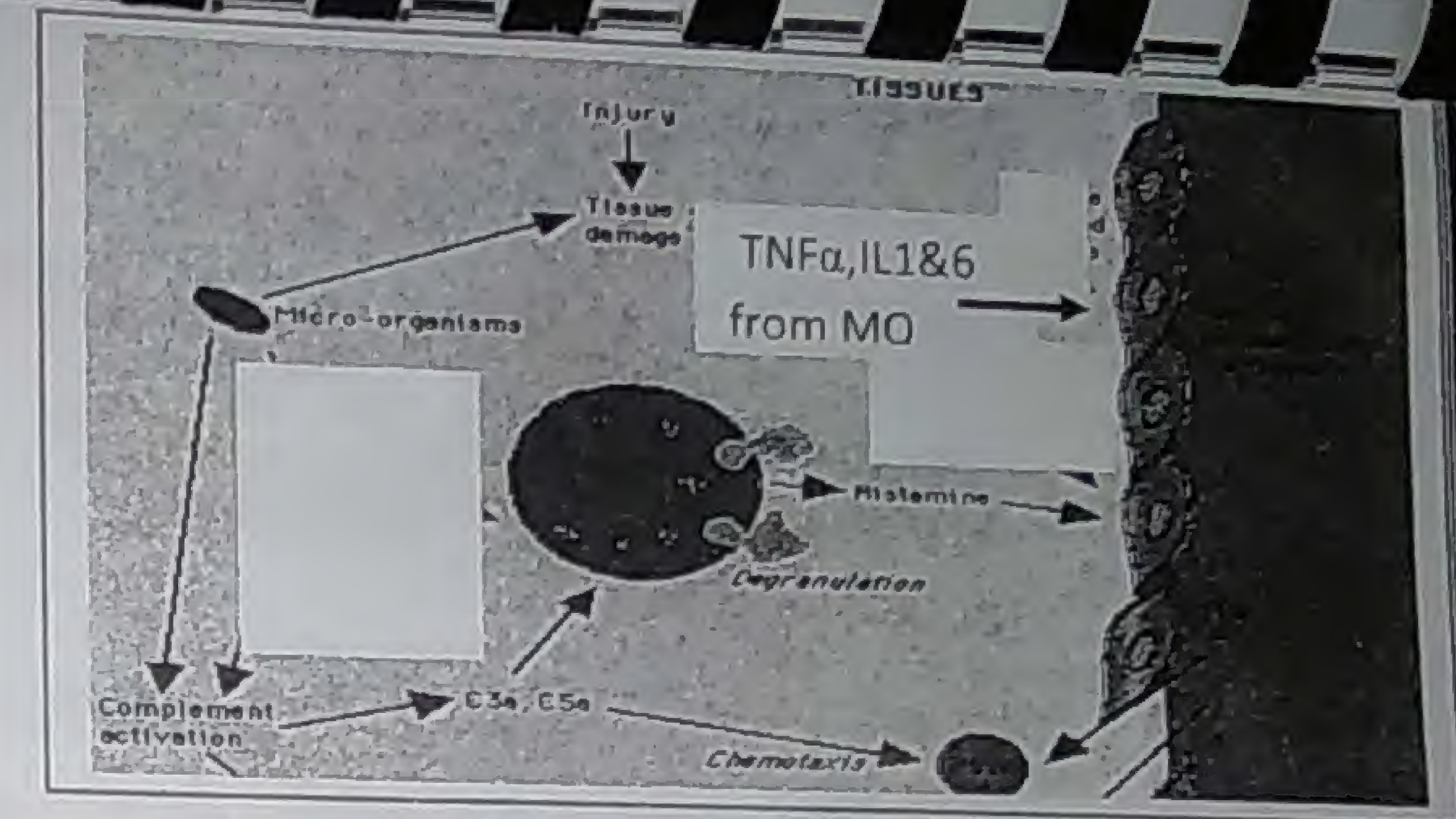
**β-Vasodilatation** : by  $TNF\alpha, IL1\&6$  (also by histamine from mast cell)

Loosening junctions between endothelial cells

Squeezing of neutrophils (*Extravasation or diapedesis*)

### C-Chemotaxis

Neutrophils migrate to site of inf. attracted by **chemotactic** substances (  $IL8$  &  $C5a$  )



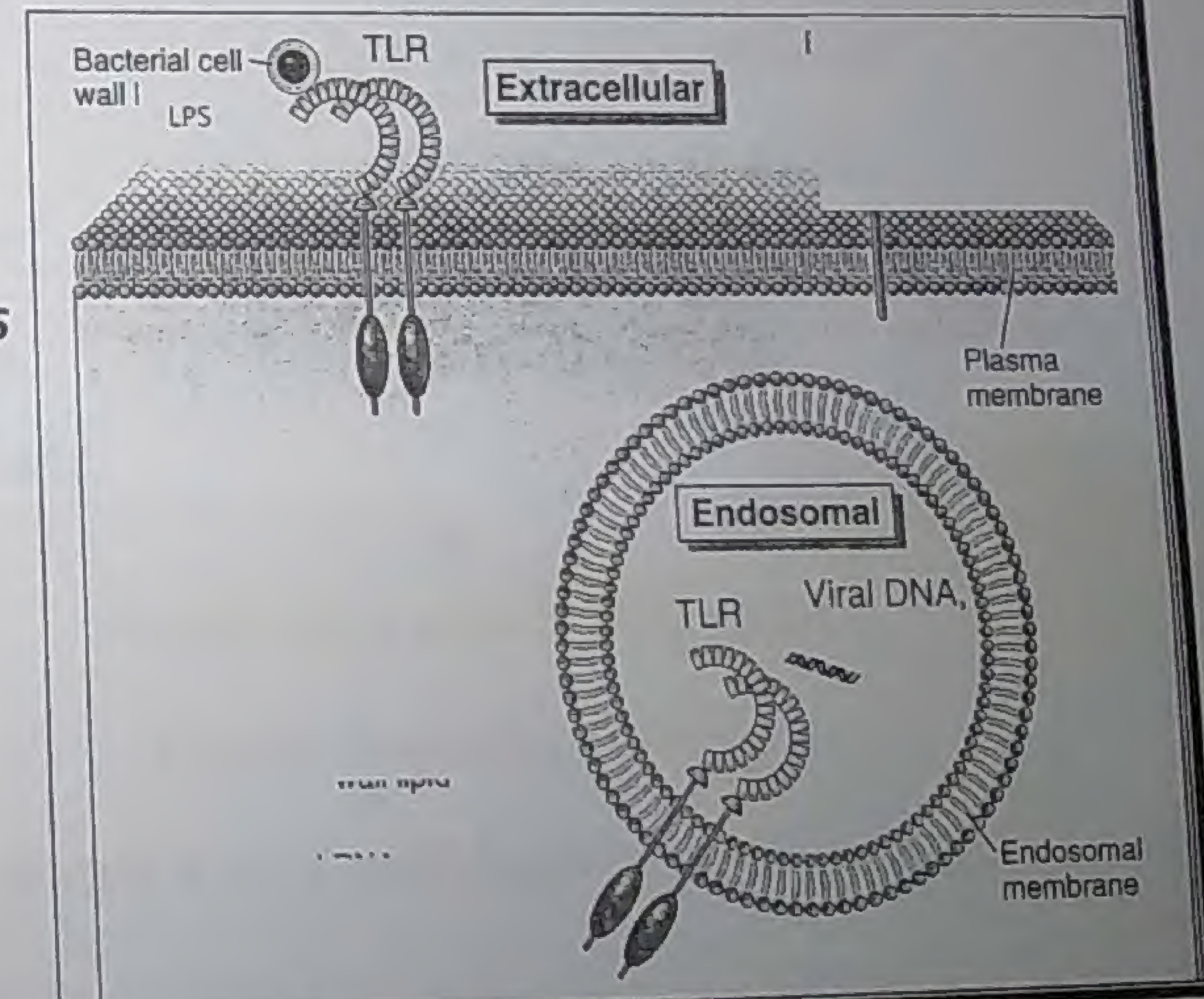
## Steps of Phagocytosis

Recognition	Uptake	IC killing	Outcome
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### 1- Recognition of microbes

by *pattern recognition receptors (PRRs)* of phagocytic cells

Site	Functions	Example
<ul style="list-style-type: none"> <li>Cell surface</li> <li>Endosomes</li> </ul>	<p><b>Recognize PAMPs</b> (pathogen-associated molecular patterns)</p> <p>Characteristic structures of microbes (not present in mammalian cells) that can't be lost or mutated</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p><b>Bacterial</b></p> <p>LPS      Teichoic acid</p> </div> <div style="text-align: center;"> <p><b>Viral</b></p> <p>DNA</p> </div> </div>	<p><b>Toll-like receptors (TLRs)</b></p>





## 2 - U p t a k e

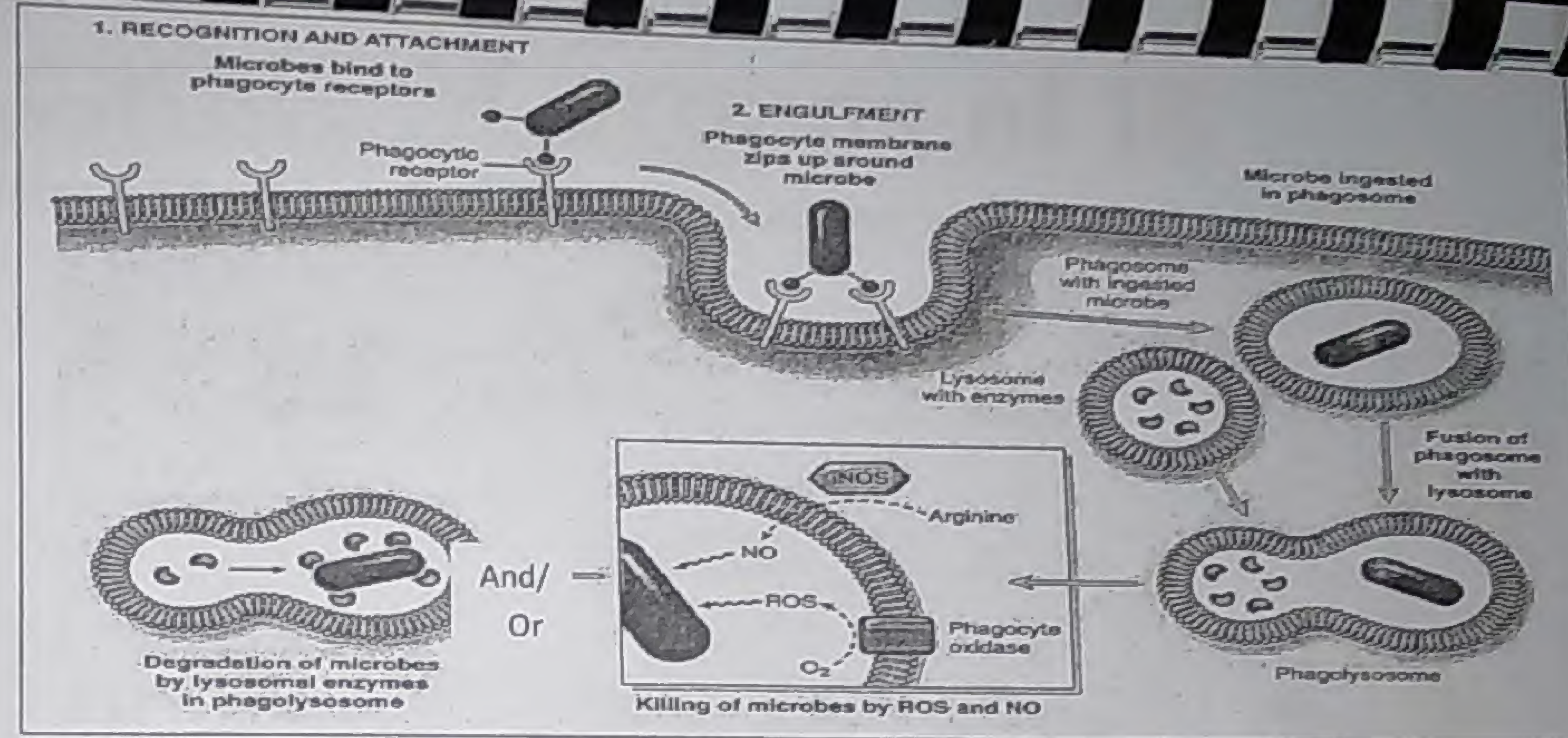
Attachement of bacterium to cell surface

↓  
Ingestion of bacterium

↓  
forming a **phagosome**

↓  
Moves towards **lysosome**

↓  
Formation of **phagolysosome**



## 3 - I C K i l l i n g

↓  
**Oxidative killing (burst)**

Molecular O<sub>2</sub>  
Myeloperoxidase ↓ Oxidase

→ O<sub>2</sub><sup>-</sup>, OH<sup>-</sup> & H<sub>2</sub>O<sub>2</sub> (ROS)

↓  
Killing of org.

--- → Produces conditions within  
phagolysosomes necessary for  
activity of proteolytic enzymes

↓  
**Non oxidative killing**

Activated MQ produce  
proteolytic enzymes  
in phagolysosomes e.g elastase

↓  
Destruction of org.

## 4- Outcome of phagocytosis

↓  
**Neutrophils**

Destroy phagocytosed particles  
completely

↓  
**Dendritic cells & MQ : APCs**

Retain fragments (Ags)

↓  
Present it to T cells (adaptive immunity)



# Classification of organs of IS

## I - Primary (Central) lymphoid organs

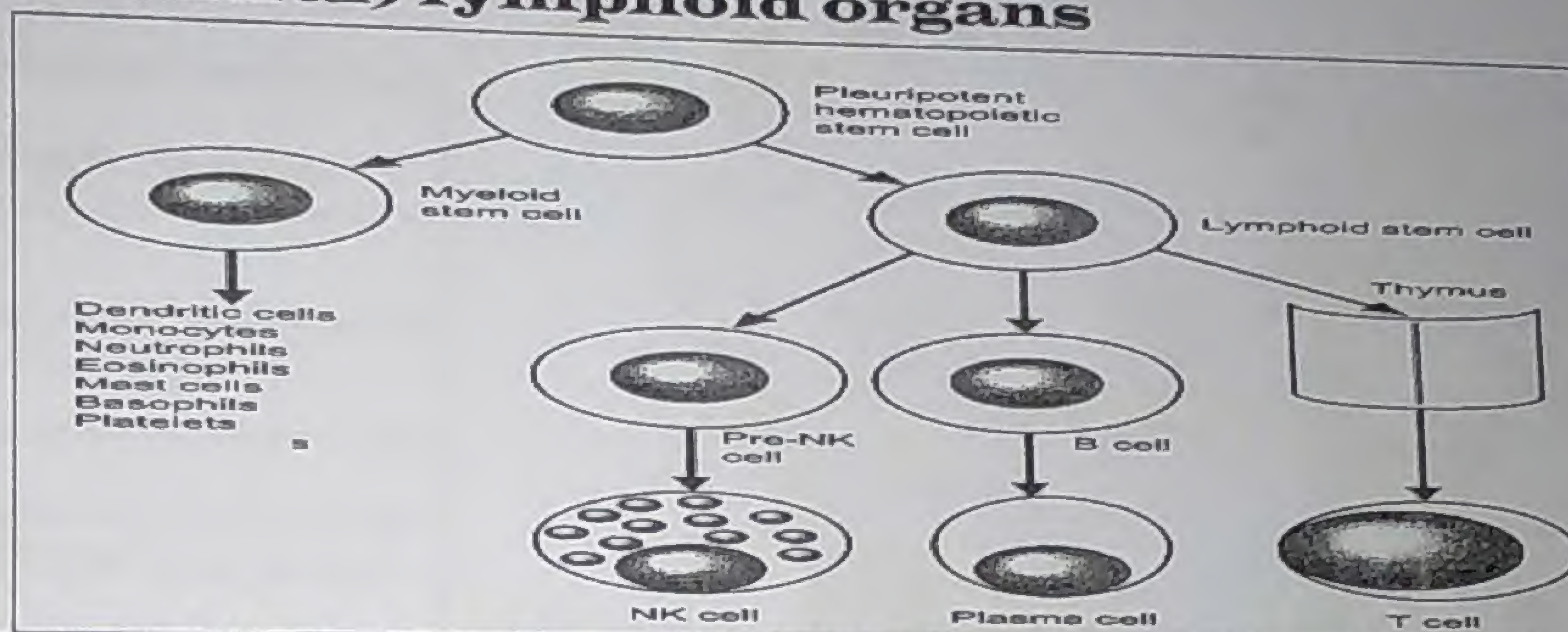
Site of development &  
maturation of immune cells

### A - Bone Marrow

#### 1-Development of all immune cells

Contains pleuripotent stem cells

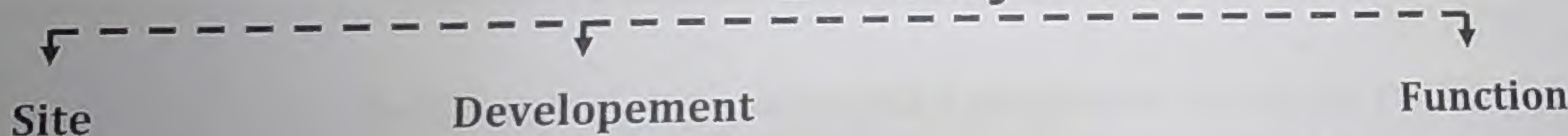
↓  
Differentiate into cells of IS



Circulating in blood		Residing in tissues		Present in tissues & blood	
• Eosinophils	• Neutrophils	Mast cells	• Dendritic cells	Lymphocytes	
• Basophils	• Monocytes		• Macrophages	• NK cells	• T & B cells

## 2 - Maturation of B cells

### B - Thymus



Site

In front of heart &  
behind the sternum

Development

Fully developed at birth

↓  
Grows until puberty

↓  
Shrinks

Function

Maturation of T cells




T cells learn to differentiate between *self* (body's own cells) &  
*non self* (foreign objects, organisms, or diseased cells)

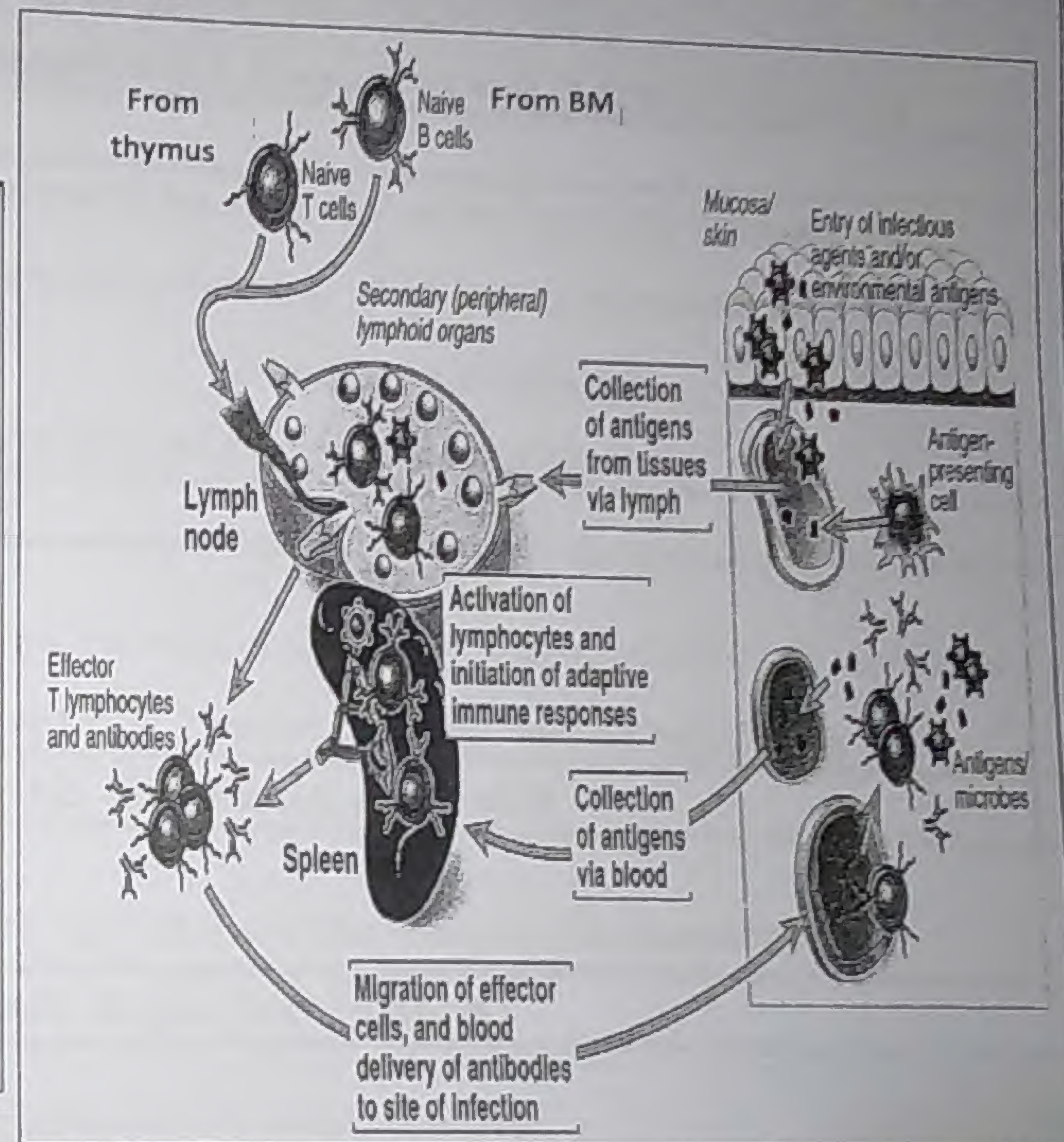
↓  
T cells recognizing self cell as foreign are destroyed



## II-Secondary (Peripheral) lymphoid organs

Sites where immune cells meet, interact & perform their functions

1-Spleen	2-Lymph nodes
A-Cellular contents	
i. MQ, dendritic cells & lymphocytes: T, B & NK cells	
B-Functions	
<b>1-Immunological filter of blood</b>  Removes any foreign material or damaged cells	<b>1-Sample incoming lymph</b> (draind from tissues)  Remove any foreign material
<b>2-Site of <math>\oplus</math> of mature (naïve) B &amp; T cells</b>  Differentiation into effector cells	



### 3-Mucosal associated lymphoid tissues (MALT)

> 50% of lymphoid tissue in the body

Diffuse collections of phagocytes & lymphocytes

In lymphoid tissue lining GIT, RT & GUT

Well formed lymphoid follicles

Tonsils, Peyer's patches & appendix



# Comparison between innate & adaptive immunity

## Innate (Natural) immunity

## Adaptive (Acquired) immunity

### 1- Time of action

Responds immediately

↓  
1<sup>st</sup> defense against infections

Takes time to be stimulated by Ags into effector cells

↓  
Provides protection when innate immunity fails  
to eradicate infection

*Both innate & adaptive immunity collaborate against any invading pathogen*

### 2- Specificity

Non specific

React to structures common to many microbes

Specific

Distinguishes between even closely related microbes & molecules

↓  
Each B & T cell reacts only with *its specific Ag*

### 3- Memory on Reinfection with the same microbe

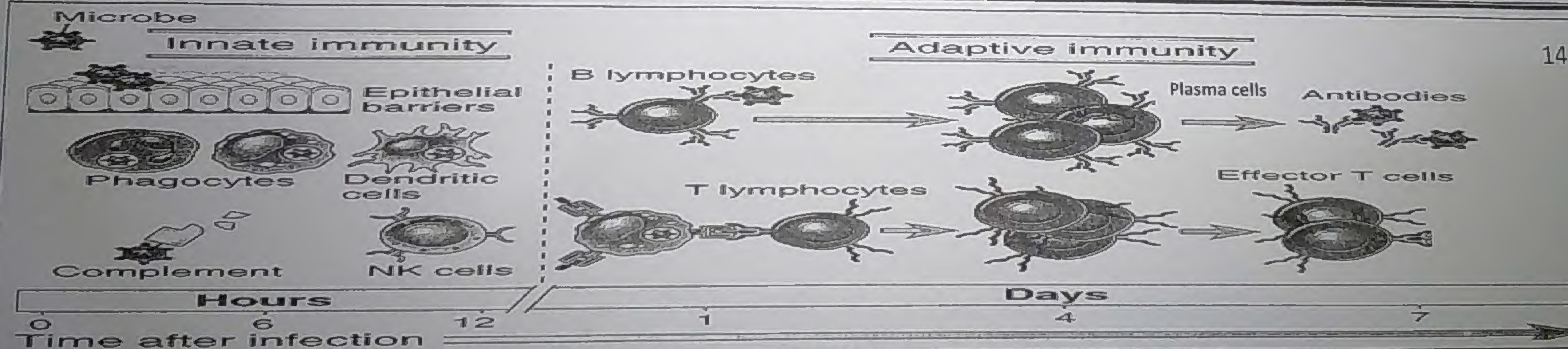
No

Response with the same magnitude

Yes

Stronger & faster response due to *memory cells*

### 4- Ability to distinguish self from foreignness





## Essay Questions

1- Compare between characters of innate & adaptive immunity.

2- How can MQ recognize pathogens ?

i. By PRRs : explain .

ii. By opsonin receptors : recognize opsonins (C3b, IgG) bound to pathogens.

3- How can MQ Kill pathogens?

4- Give a short account on sources & functions of IL1 OR TNF  $\alpha$  , OR IL6

5- Give reason :

- Normal bacterial flora are part of innate immunity
- Recruitment of neutrophils from BVs to site of infection



# Immunology 2

Cell Mediated Immunity

Cell Mediated Immunity



# Cell mediated IR & T cells

T cell developement	MHC molecules	Th & Tc activation	Cytokines Regulating CMI	Down regulation of IR	Immunity against microbes	Pathological effects of CMI	Deficiency of CMI
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## T lymphocytes development & Differentiation

### I-Origin of T cells

From stem cells in BM

Circulate in blood as immature thymocytes with no surface markers

ظاہر ہے

### II-Maturation of T cells: in thymus

#### A-Structure of thymus

Outer cortex

Packed with  
*immature T cells*

Inner medulla


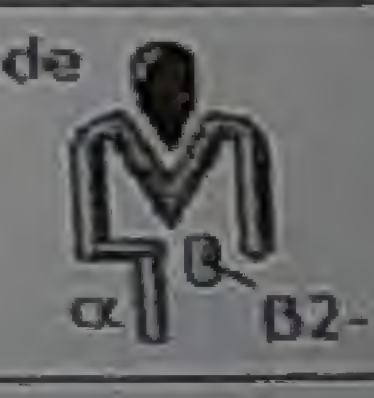
T cells pass into it  
*during their maturation*

Both are packed with a network  
formed of epithelial cells, MQ & DCs  
Interact physically with thymocytes

CD molecules  
(cluster of differentiation)  
♦ Surface markers  
given numbers : 1,2,3,4.....  
♦ Each immune cell  
has specific CDs

### B-Thymocytes differentiation

Thymocytes differentiate into 2 types of T cells

	<b>T helper (Th) : CD4+ cells</b>	<b>T cytotoxic(Tc) : CD8+ cells</b>
1-% of circulating T cells	60-65%	30-35%
2-Surface markers	a-TCR complex : i.T cell receptor (Ag R) ii.CD3	
	<i>b-CD4</i>	<i>b-CD8</i>
3-MHC restriction	Recognize Ag only in association with MHC <i>class II</i>	Recognize Ag only in association with MHC <i>class I</i>
	Peptide  $\alpha$ $\beta$	Peptide 1  $\alpha$ $\beta 2-m$



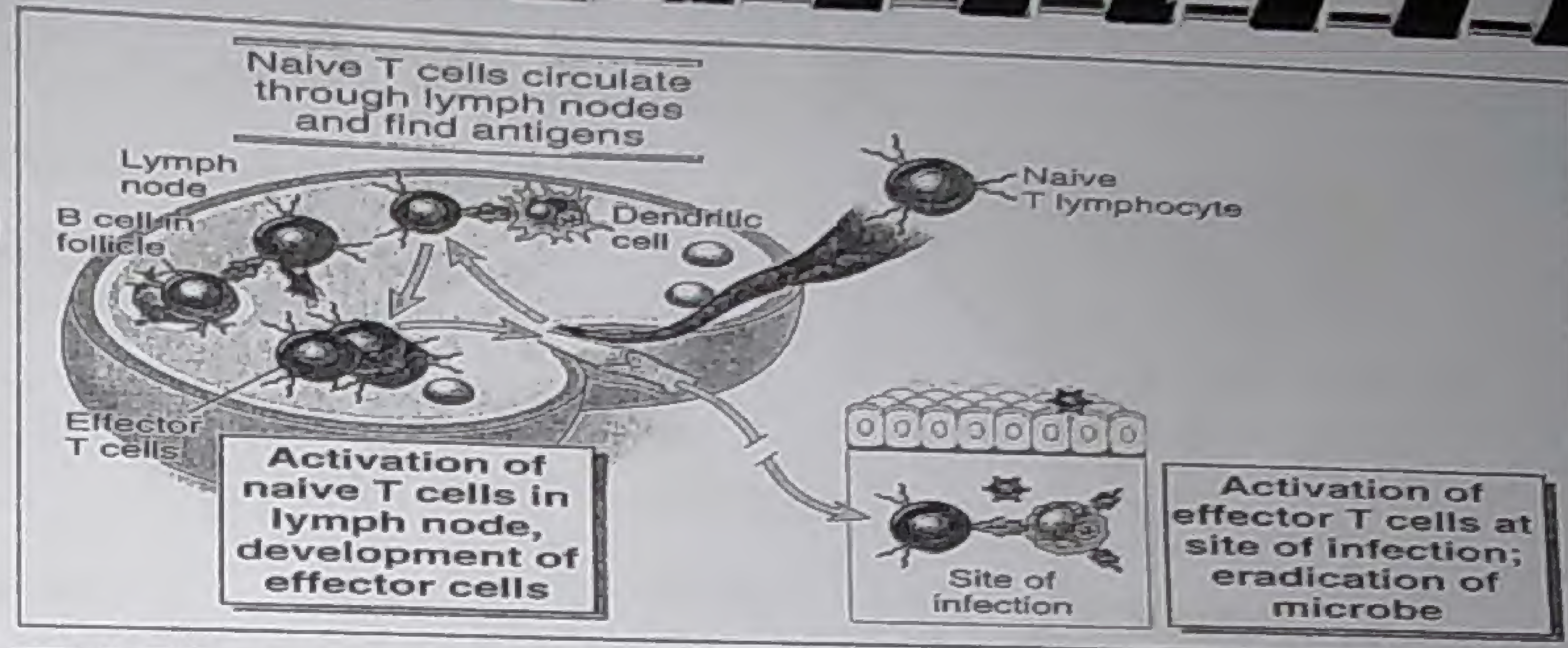
### III-Release of T cells

Mature T cells released from thymus are cd  
naïve lymphocytes ( have never encountered Ags)

↓  
Circulate to 2ry L.O

to be ⊕ by professional APCs

( MQ, dendritic cells & B cells)



### IV- Clonal expansion & Differentiation of T cells into

↓  
Effector cells

↓  
Memory cells

↓  
Effector *CD4+* cells : *Th1&Th2*

↓  
Effector *CD8+* : *CTLs* (Cytotoxic T lymphocytes)

↓  
Memory

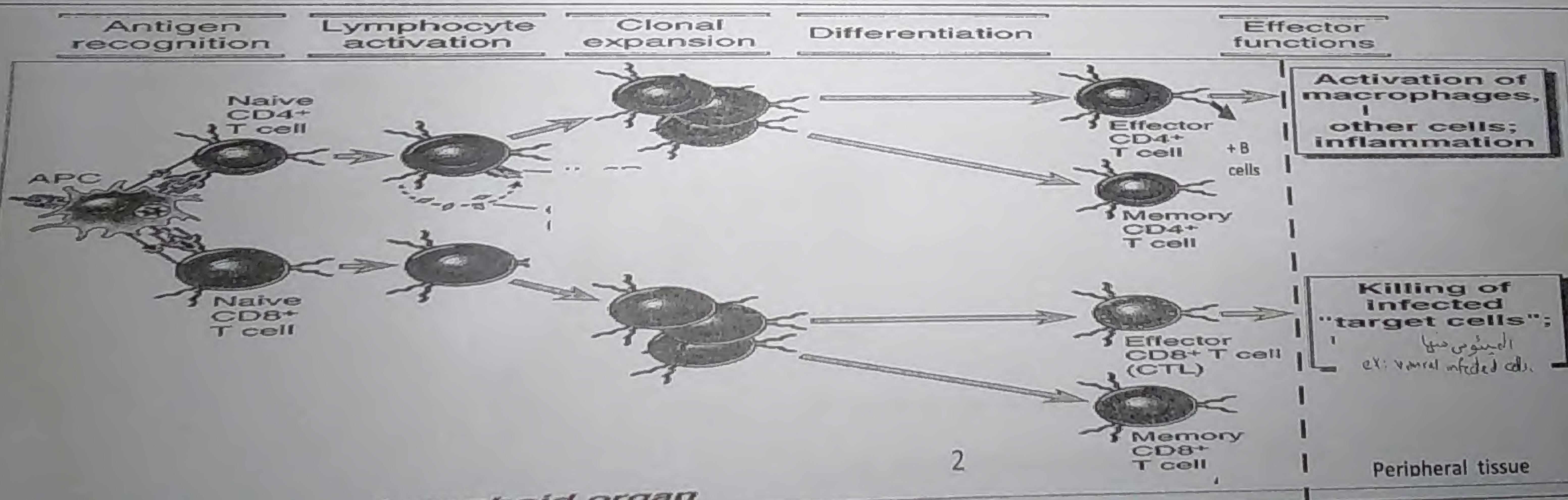
↓  
Memory

↓  
Produce cytokines that ⊕ MQ & B cells

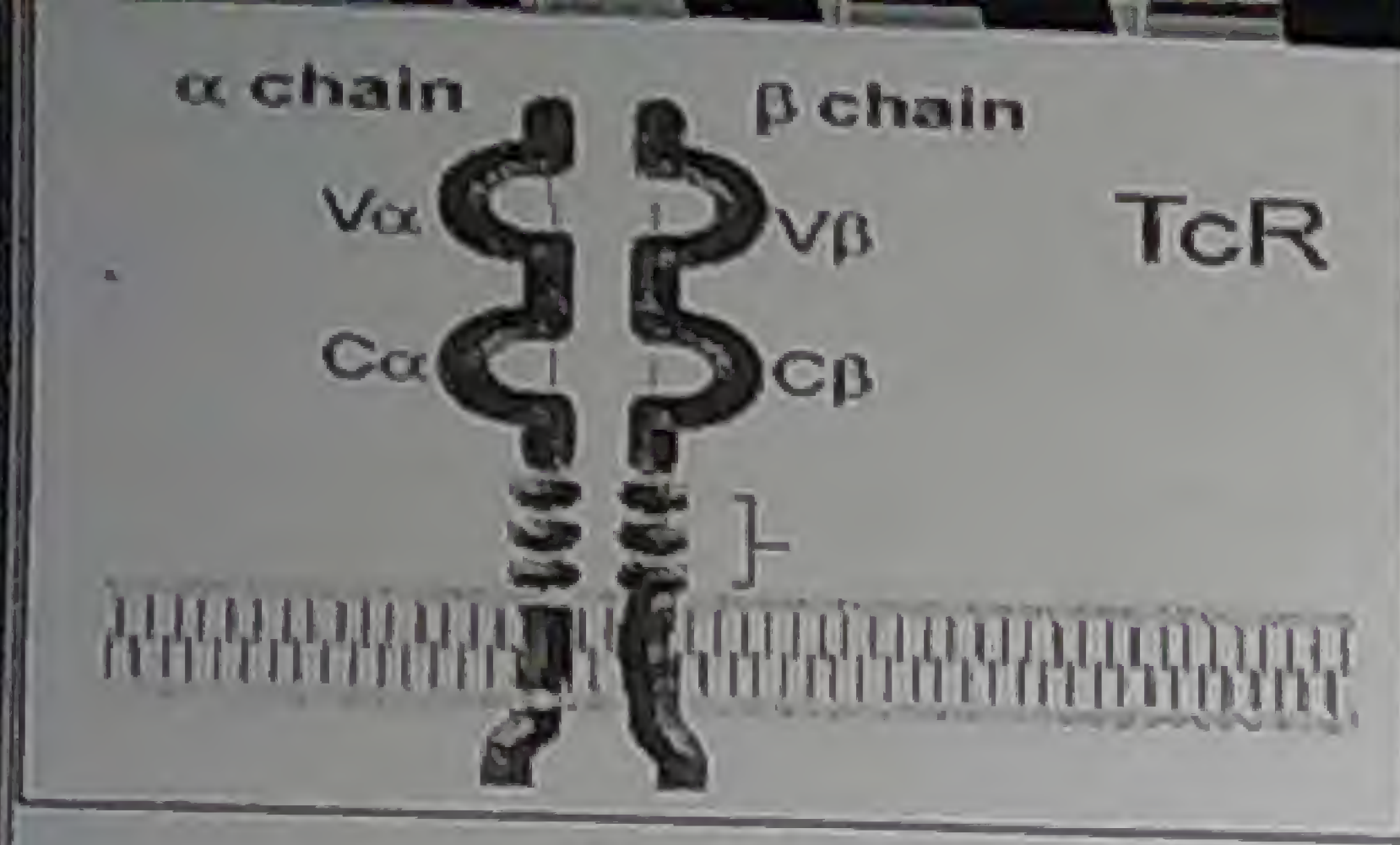
↓  
Kill infected cells

CD4+

CD8+







# TCR COMPLEX

## I - T cell receptor (TCR)

### A-Structure & Diversity

#### Structure

Formed of  $\alpha$  &  $\beta$  polypeptide chains having :

#### C region

Anchored to CM & extends into cytoplasm

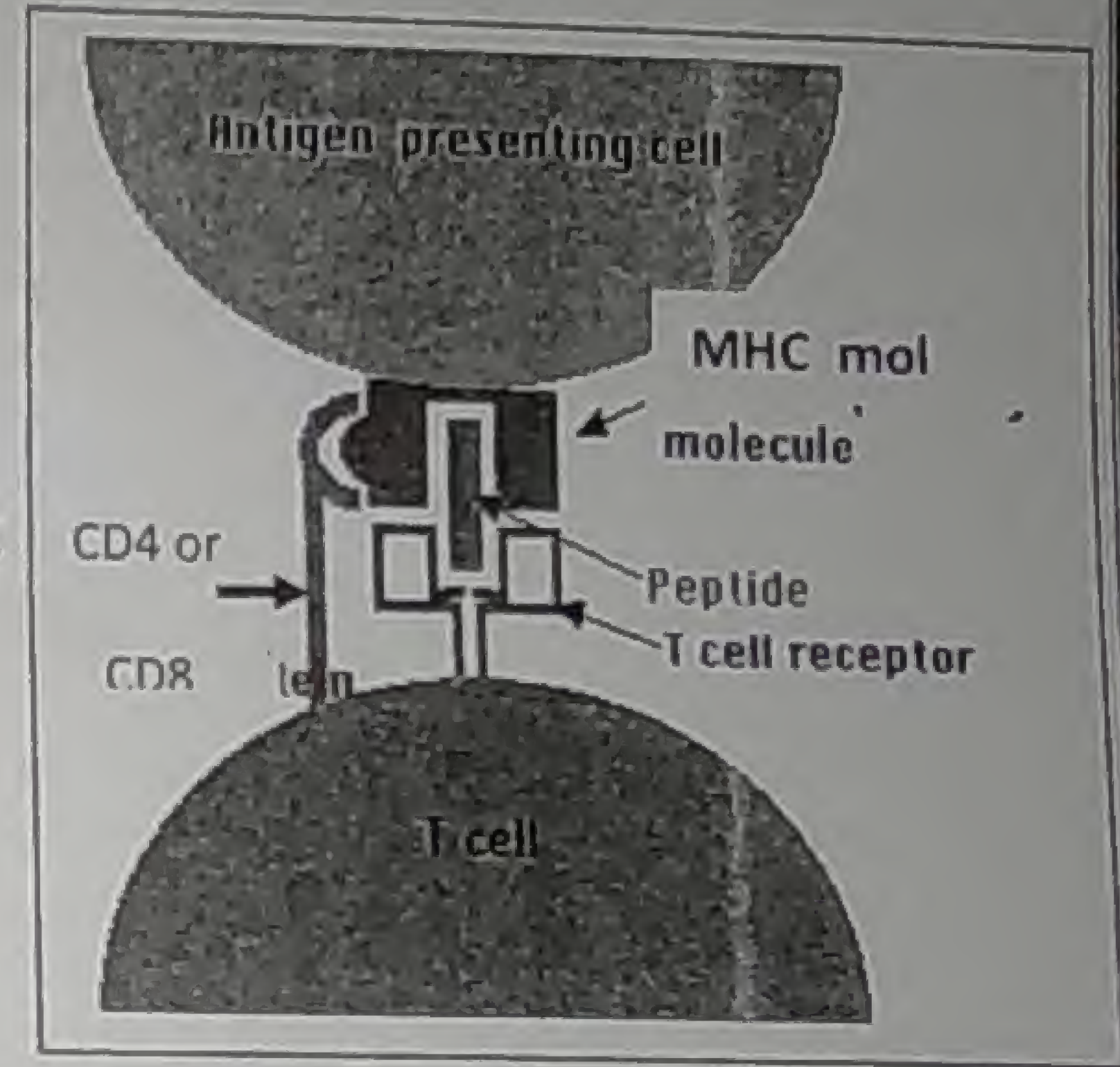
#### V region recognizes

Specific peptide Ag (Complementary to it) **MHC mol**  
{ Lock & Key }

#### Diversity

do differ in variable region  
تم صنع مليون قتيل قبل السرطان لا يفتاح

Millions of T cells exist  
React with millions of different peptides of Antigena

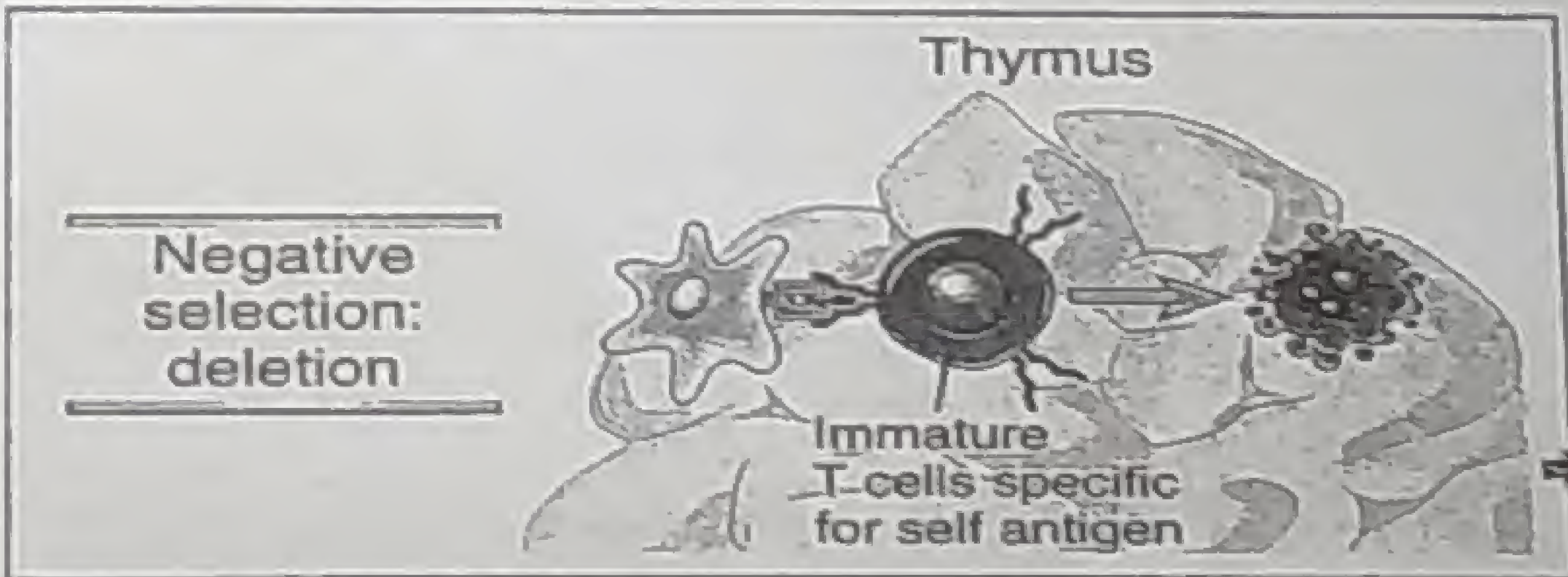


### B-Positive & Negative selection

#### + ve selection

T cells expressing TCR that recognize self MHC mol. **are selected to survive**

TCR expressing TCR that don't recognize self MHC mol. **die by apoptosis**



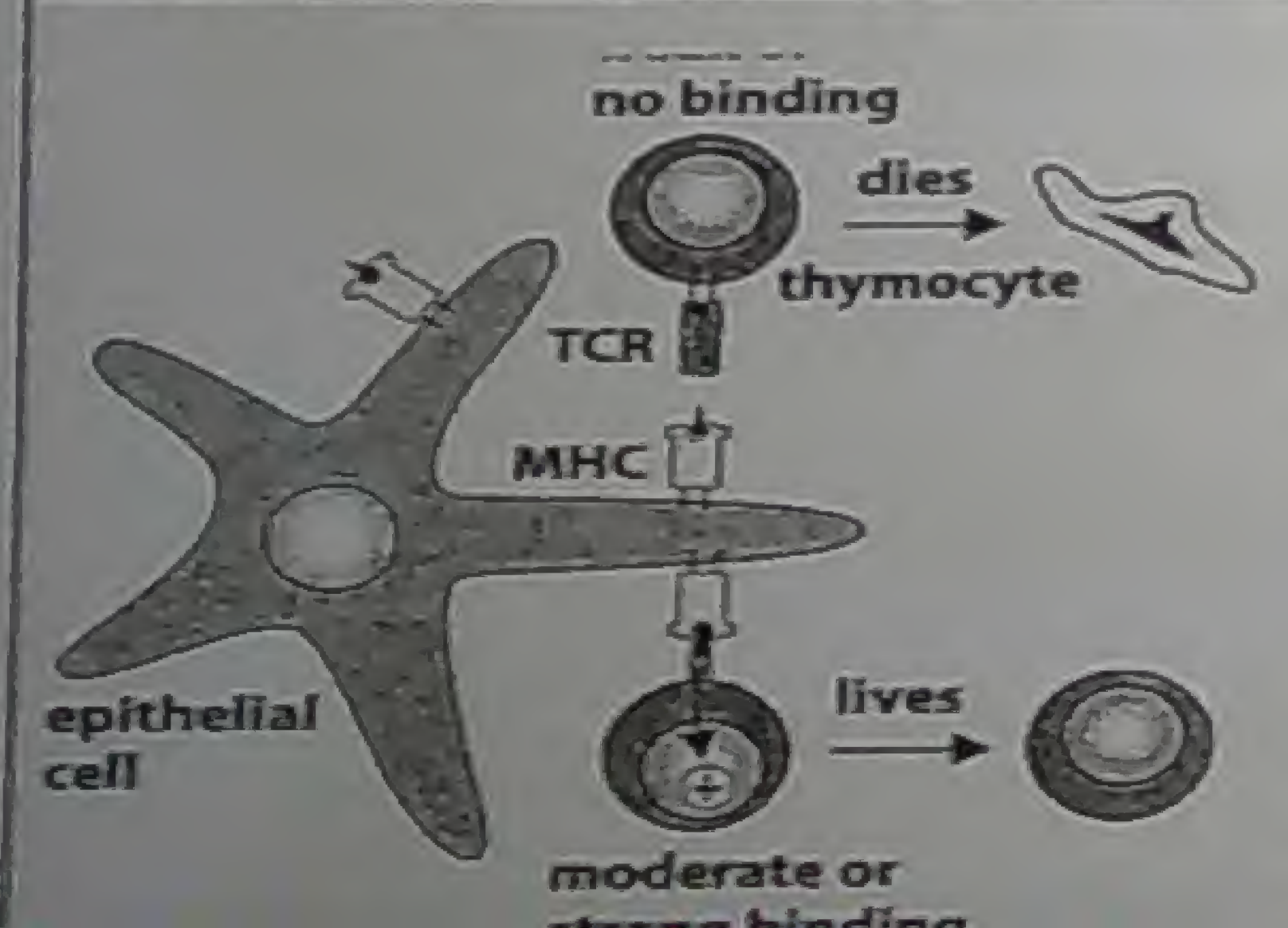
#### -ve selection

T cells expressing TCR that can react with self peptides (self reactive cells) **are killed by apoptosis**

#### Self tolerance

no reaction against self antigene  
No autoimmune reactions

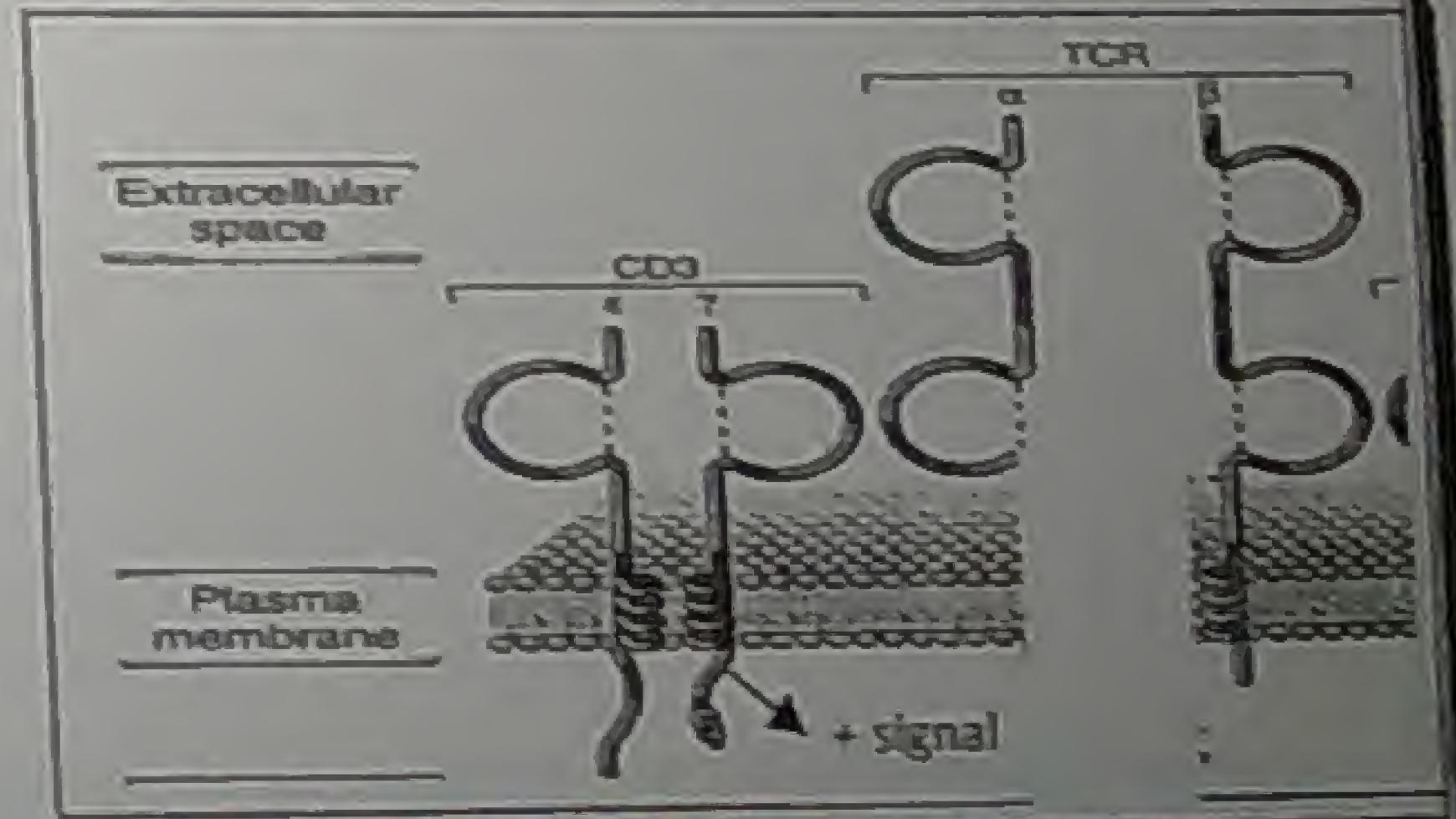
#### Positive selection of $\alpha\beta$ T cells by cortical epithelial cells in the thymus



## II-CD3

Associated with TCR

Transmits signal from outside to inside  
( informs that Ag receptor is occupied)





# Self mol. : Major histocompatibility (MHC) or human leukocyte Ags (HLA)

Definition

Site

Structure

Inheritance

Importance

Role in Ag presentation

## Definition

Are special inherited self proteins on surface of nucleated cells رَبِّي الدِّهْمِيَّة

↓  
Distinguish one individual from another

## Site

### MHC class I mol.

All nucleated cells (including professional APCs)

❖ Absent on RBCs

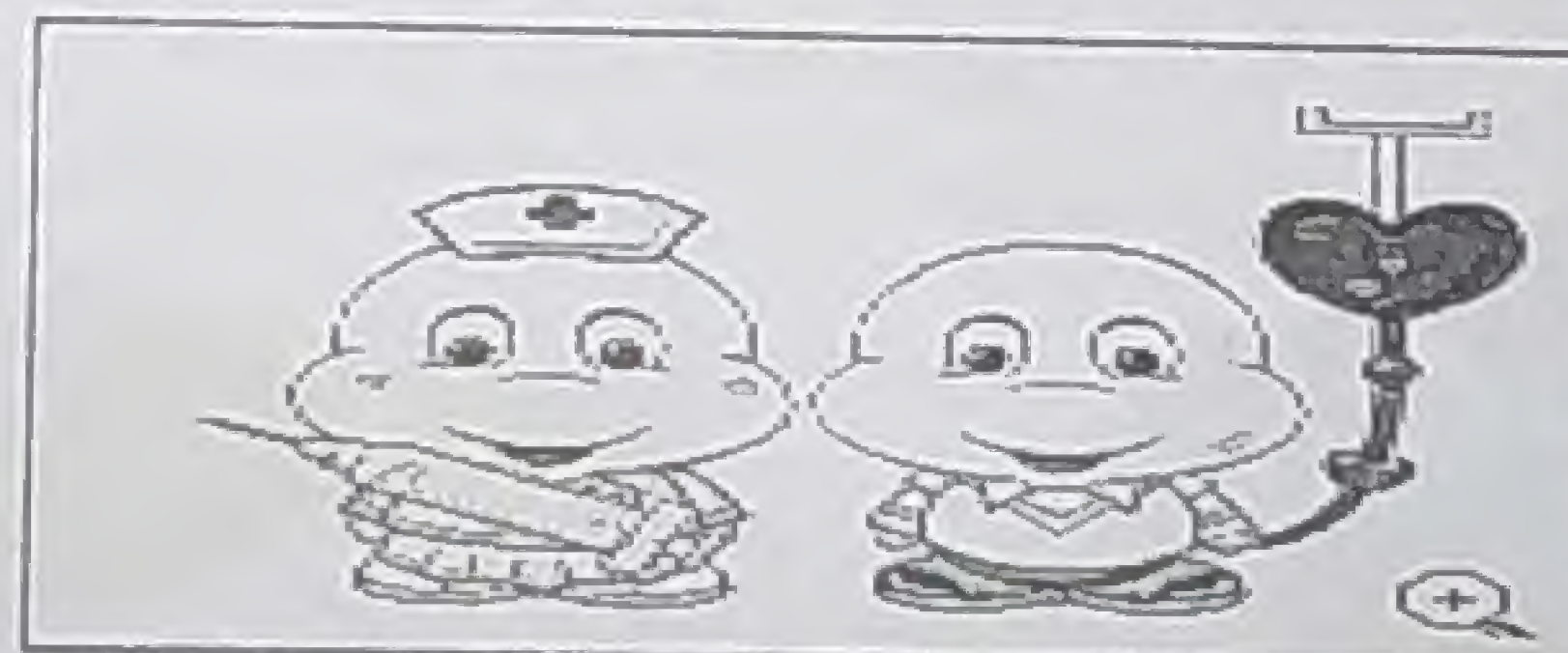


Possible blood transfusion

❖ ↓ levels on sperms & trophoblasts



Possible conception & child bearing  
(mother doesn't reject genetically different paternal cells or fetus)



### MHC class II mol.

Professional APCs

♪ MQ

♪ Dendritic cells

♪ B cells



# Structure

## MHC class I mol.

## MHC class II mol.

1-Each mol.(protein) is formed of 2 polypeptide chains :  $\alpha$  &  $\beta$   
(non covalently linked)

i .  $\alpha$  chain : 3 domains ( $\alpha_1$ ,  $\alpha_2$  &  $\alpha_3$ )

i .  $\alpha$  chain : 2 domains ( $\alpha_1$  &  $\alpha_2$ )

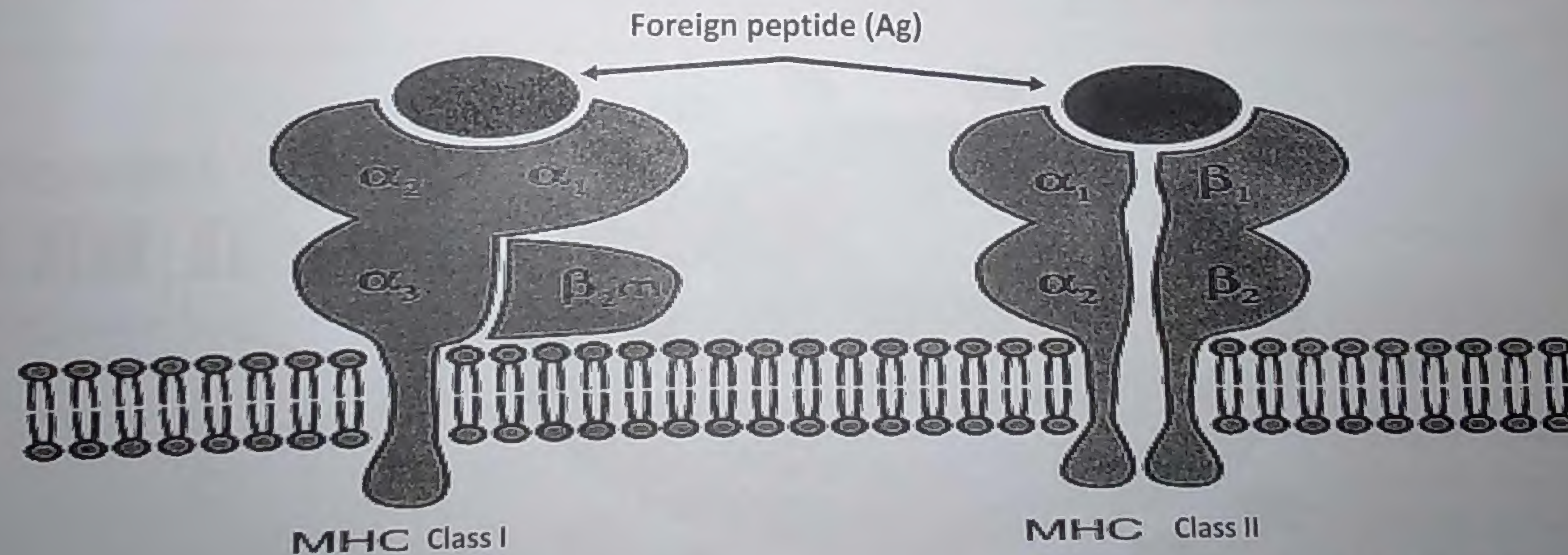
ii .  $\beta_2$  microglobulin

ii .  $\beta$  chain :  $\beta_1$  &  $\beta_2$

2- Ag (peptide) binding site

Between  $\alpha_1$  &  $\alpha_2$

Between  $\alpha_1$  &  $\beta_1$





# Inheritance of MHC proteins

## MHC Class I mol.

## MHC Class II mol.

1- MHC proteins are coded by multiple genes on short arm of chromosome 6

3 genes : **A, C & B**

3 genes : **DR, DQ & DP**

2- Each person has 2 sets of these genes : 1 paternal & 1 maternal

3- Alleles inherited from both parents are codominantly expressed in each individual

4- MHC genes are **the most polymorphic genes** in human genome

**A gene** : 240 alleles   **B gene** : 470   **C gene** : 110

**DR gene** : 350 alleles

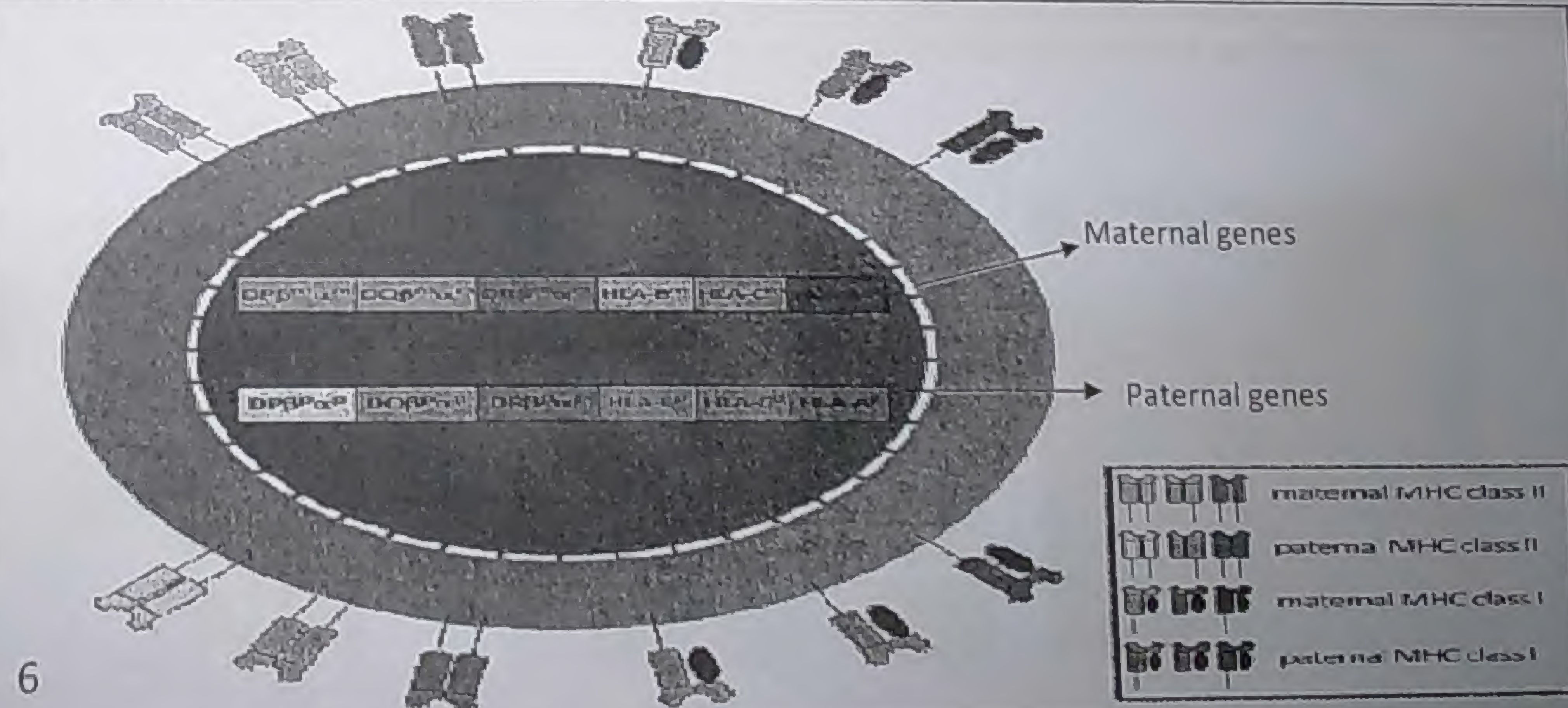
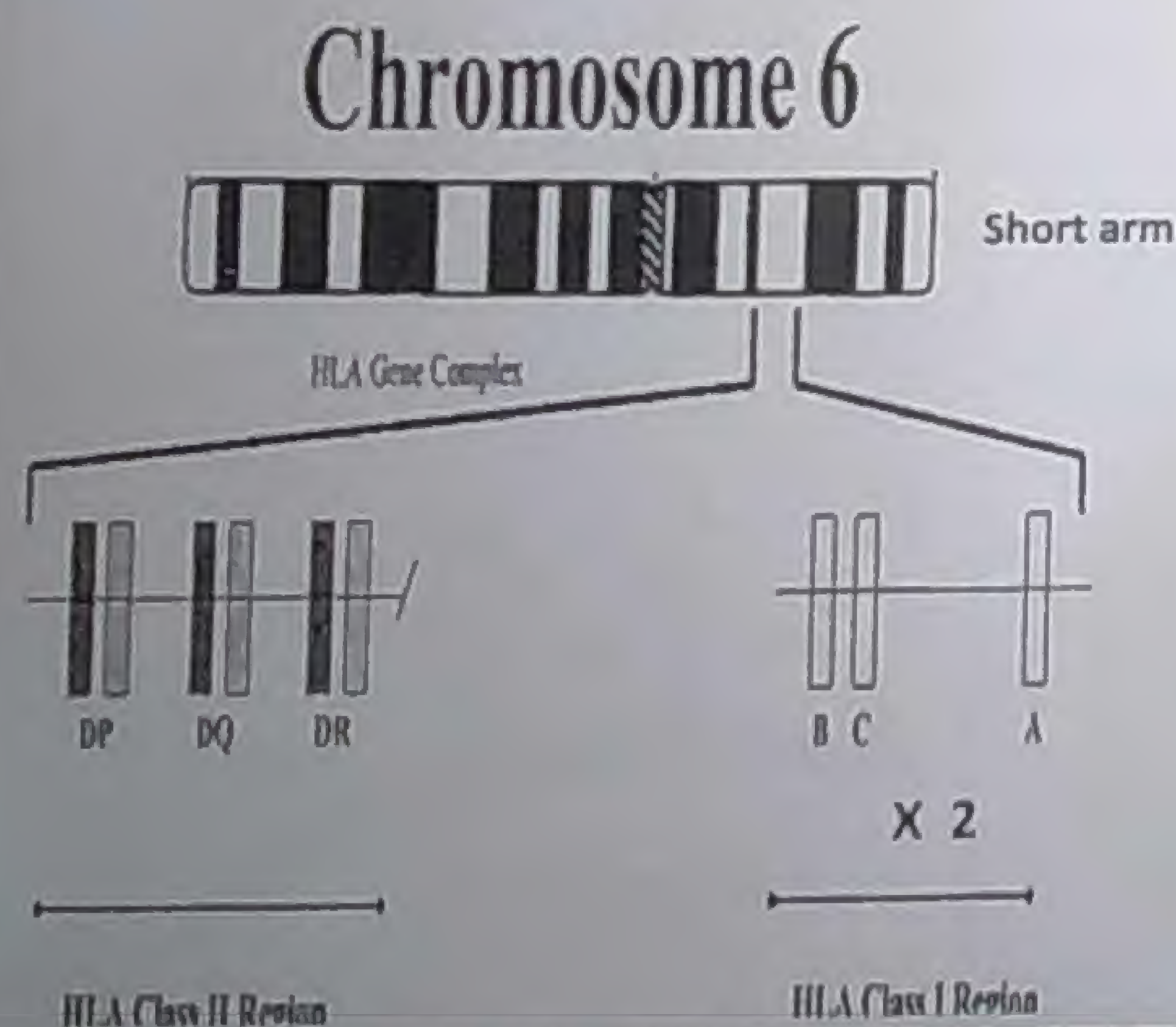
↳ different form of same gene

5- Outcome of MHC gene expression in different individuals

Synthesis of polypeptide molecules :

i. Different in amino acid sequence

ii. Carry same function ⇒ can not load peptide.

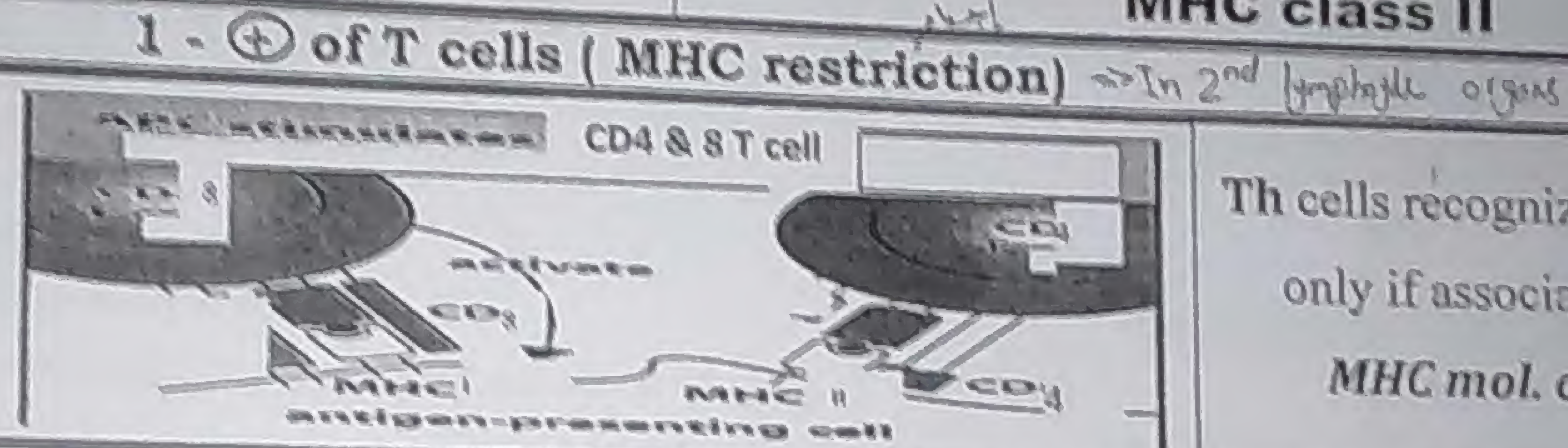




# Importance of MHC mol. in health and disease

## MHC class I

Tc cells recognize foreign peptide only if associated with **MHC mol. Class I**



## MHC class II

Th cells recognize foreign peptide only if associated with **MHC mol. class II**

## 2 - Rejection of transplanted organs

Foreign MHC class I & II on donor tissue transplants are recognized by IR of recipient

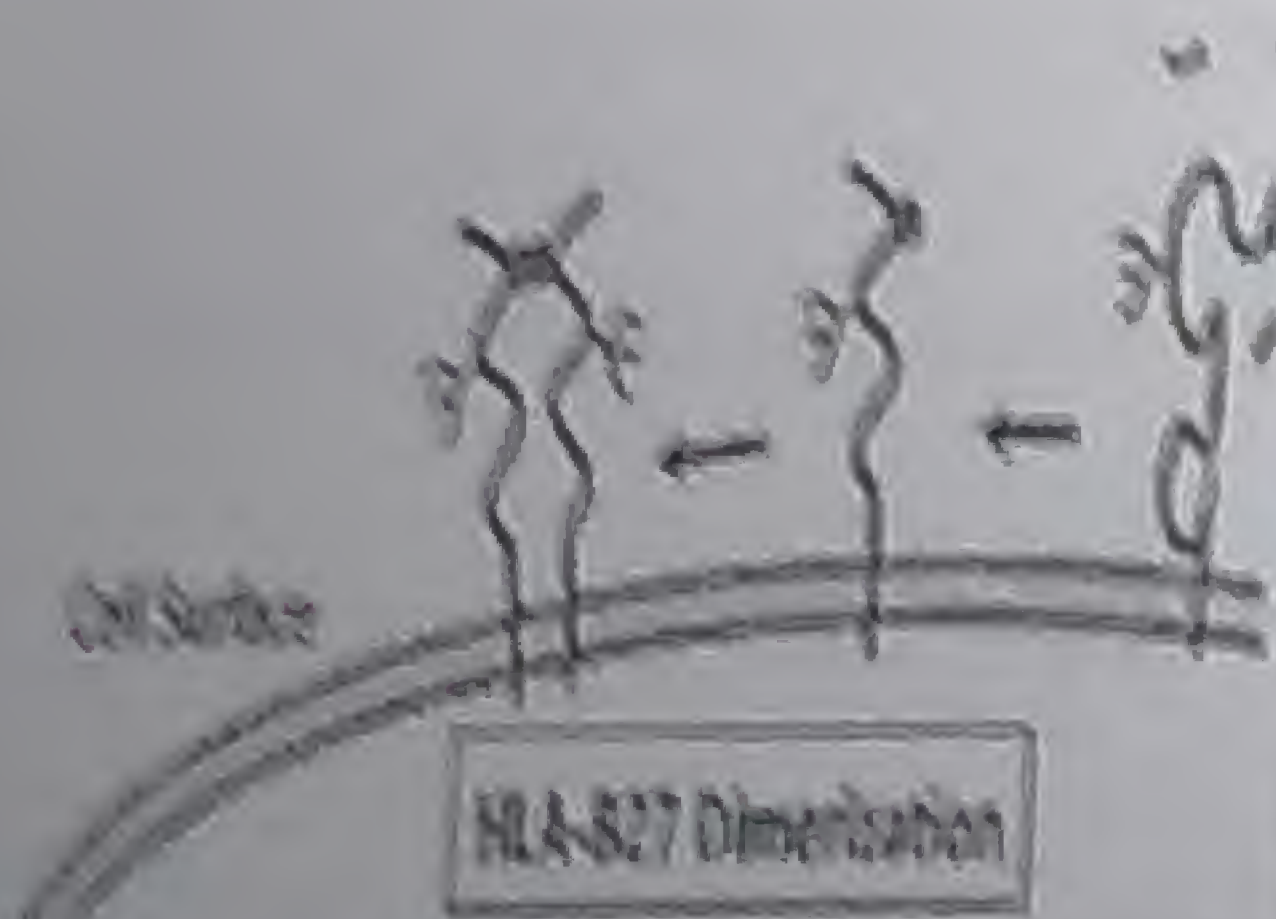
Transplant *killing & rejection*

MHC mol. must be closely matched as possible between donor & recipient

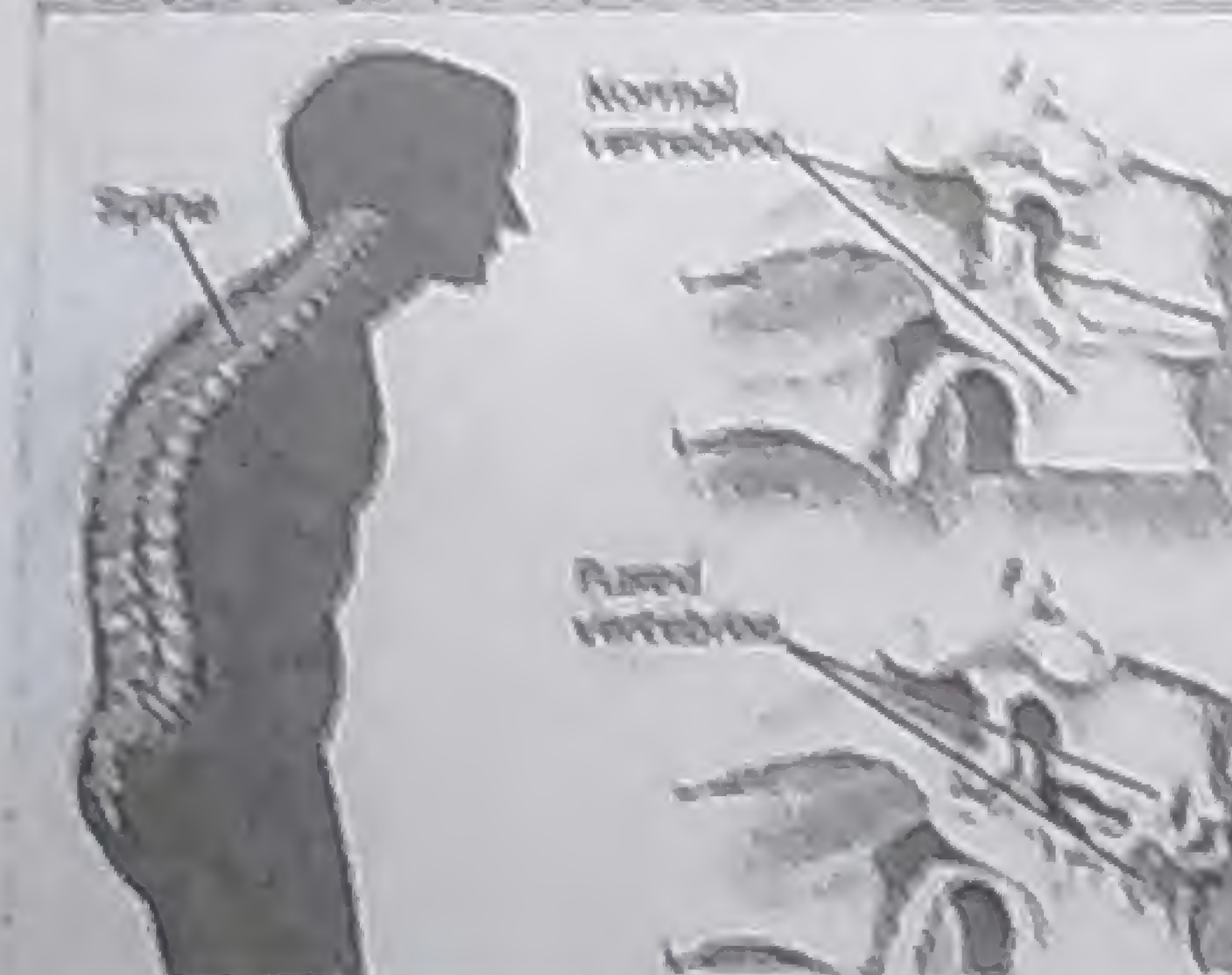
## 3-Association of some MHC alleles with certain autoimmune diseases

**B27** in 90% of pts with ankylosing spondylitis

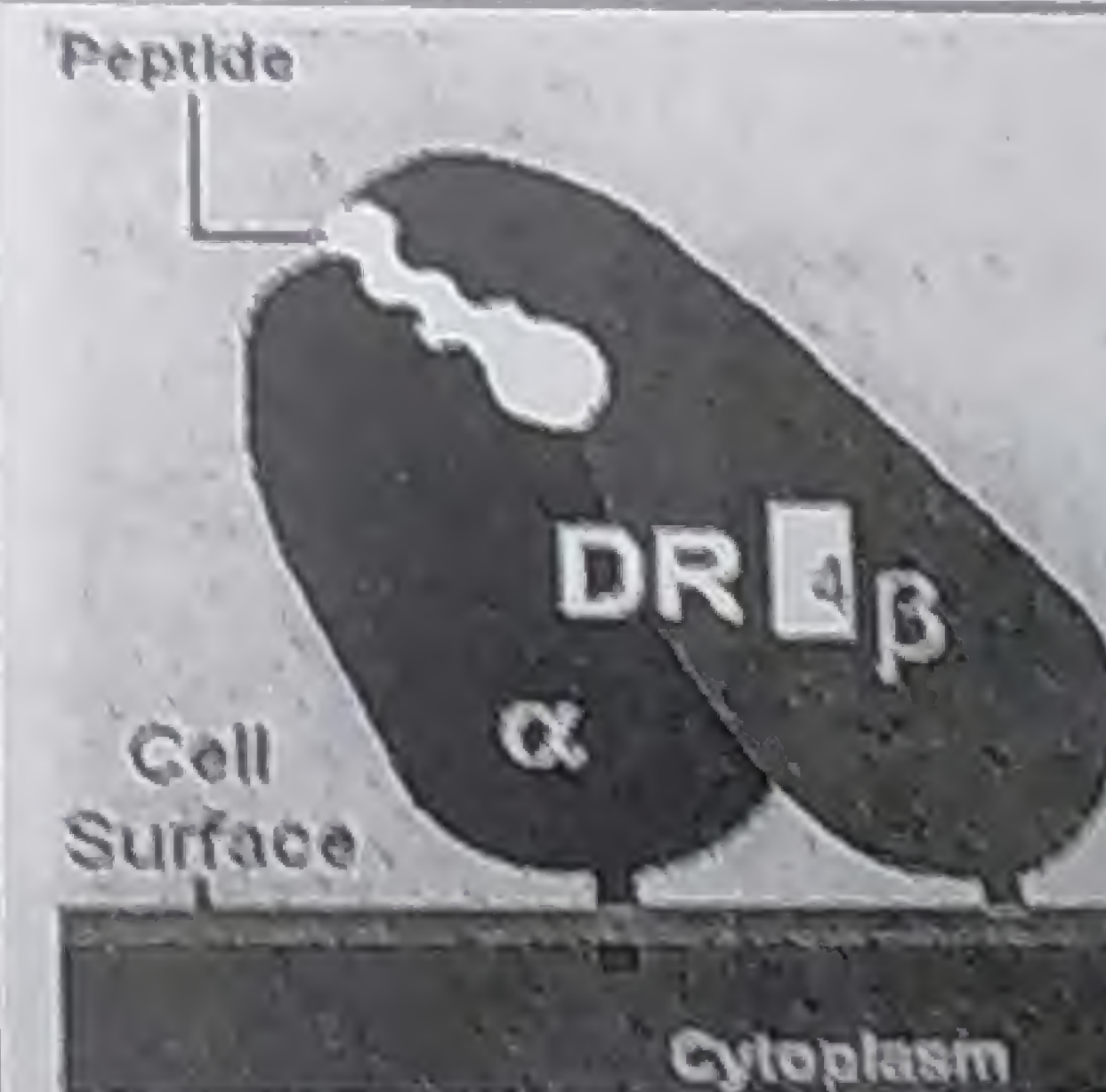
(B27 is present in only 10% of normal persons)



Ankylosing Spondylitis



**DR4** in pts with rheumatoid arthritis





# Functions of APCs

1- Recognize any microbe via PAMP receptors ( PRR)

Phagocytose & kill it (phagocytic cells)

2-Inflammation

Acute inflammatory response

TNF $\alpha$  , IL 1 & 6

Chemotaxis of neutrophils & T cells

IL 8

3-Activation of T cells : by

Ag presentation

Digest phagocytosed particle

into fragments

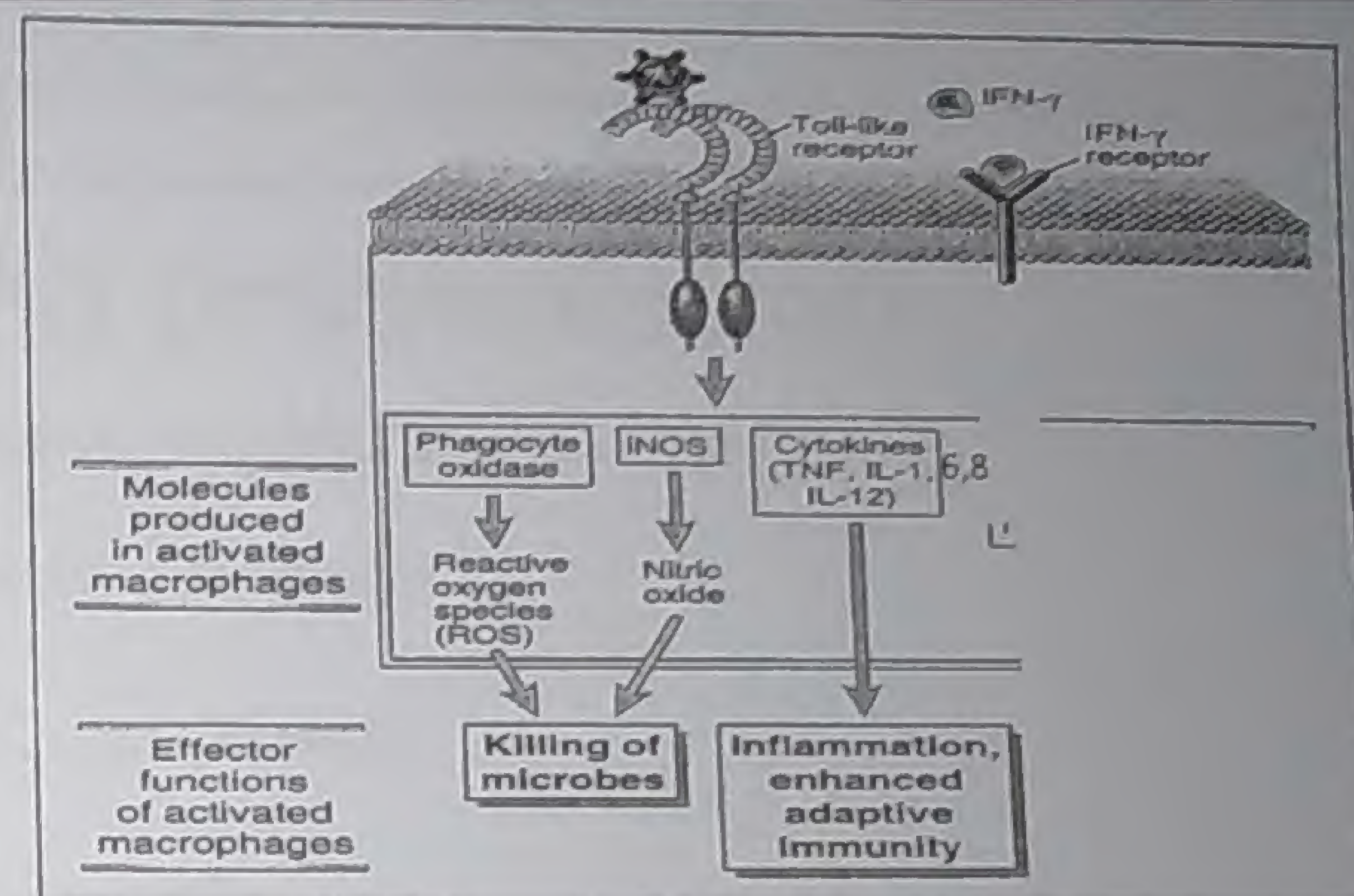
( by special enzymes)

Fragments are associated with

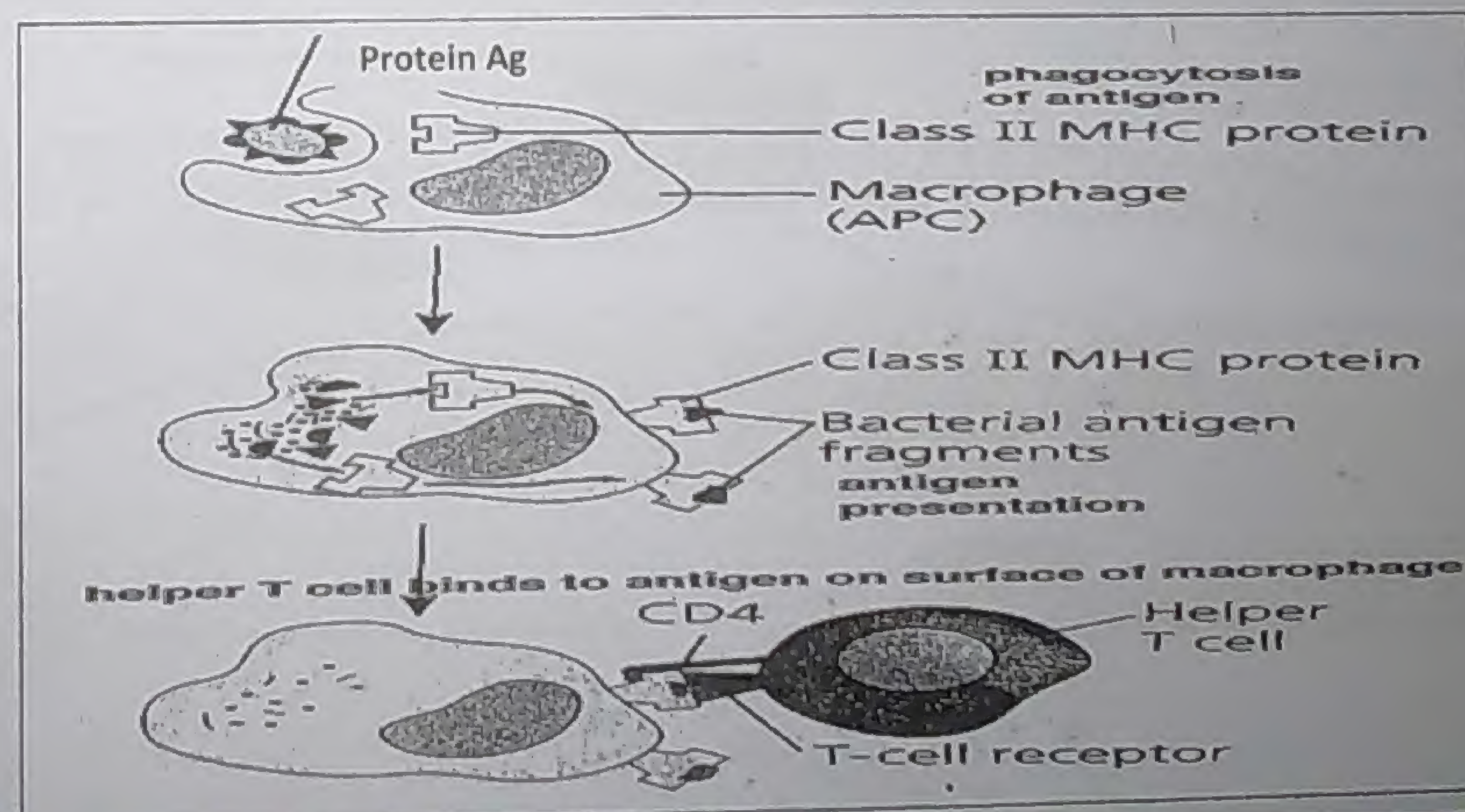
MHC class II mol.

Transported & displayed on cell surface

Recognized by CD4+Th cells



Production of IL 1 ( $\oplus$ Th) & IL 12 (induce formation of Th1)





# CD4 T helper phocytes (Th)

Role of MHC class II

Activation

Anergy

## Role of MHC class II in Ag presentation

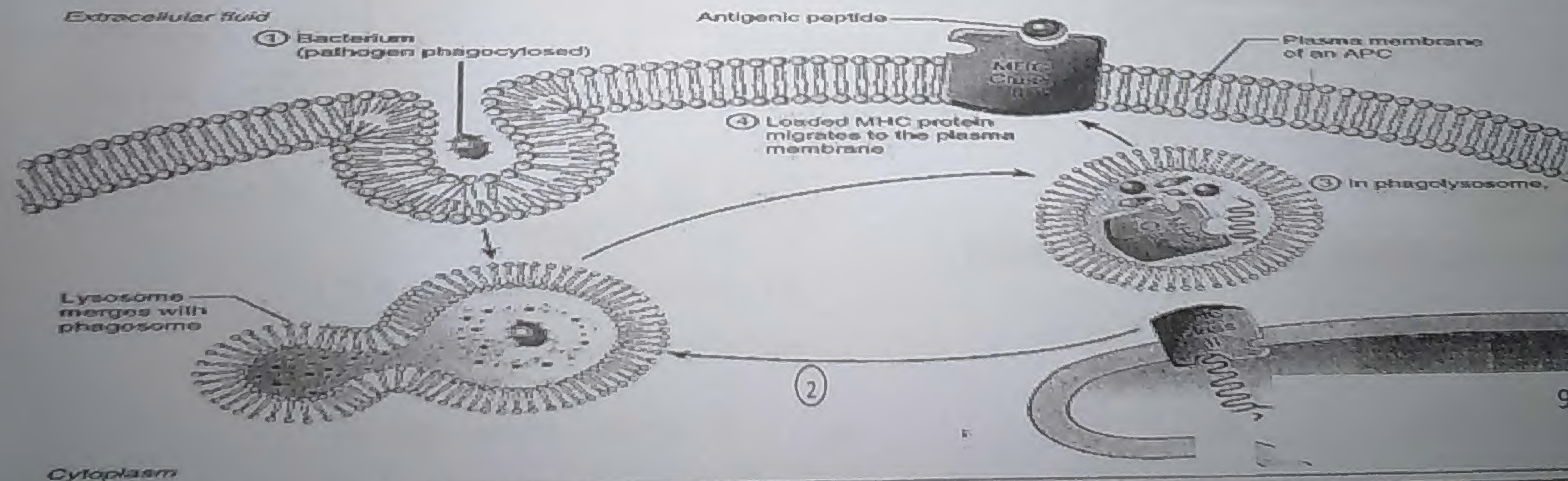
Professional APCs (MQ, dendritic and B cells) ingest microbial proteins (Ags)

↓  
Degrade (chop) it into fragments (peptides) by enzymes

↓  
Fragments are associated with MHC class II mol.

↓  
Transported & displayed on cell surface

↓  
Recognized by CD4+Th cells

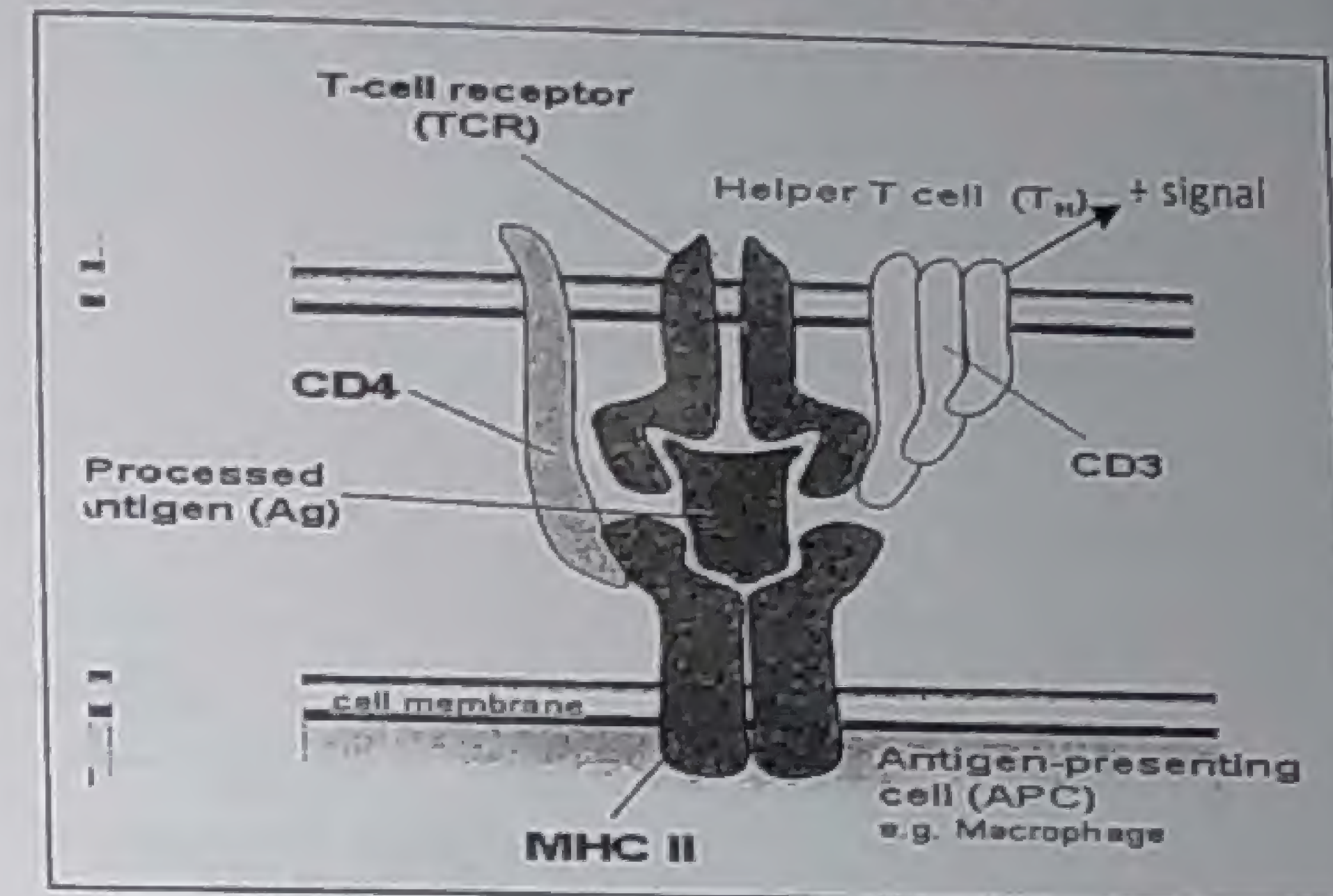
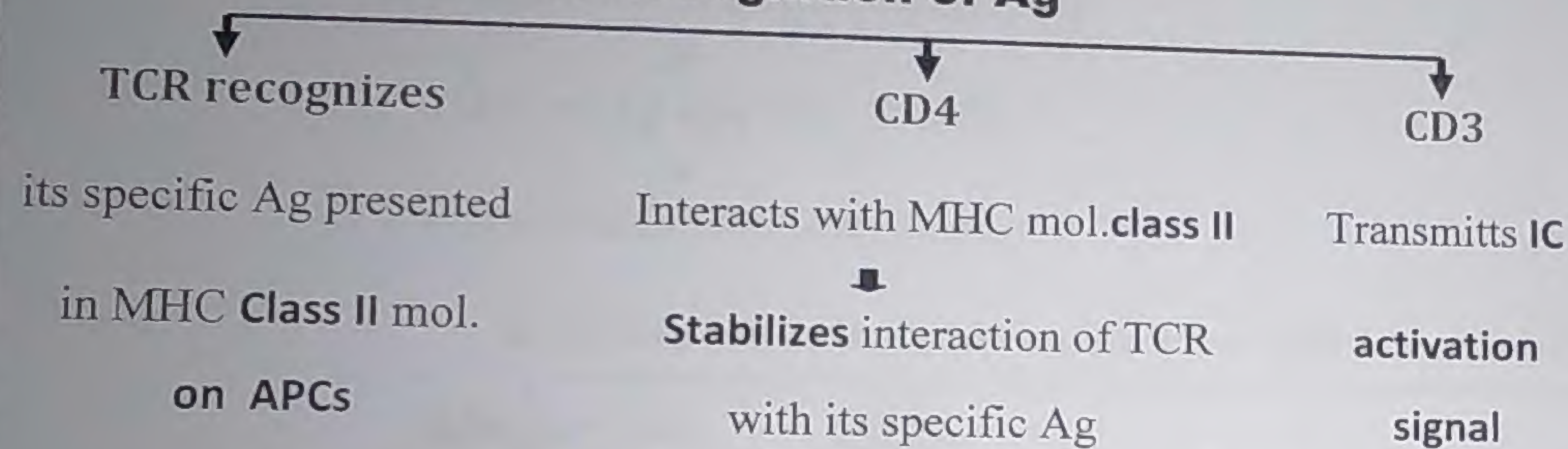




# Activation of CD4 Th cells

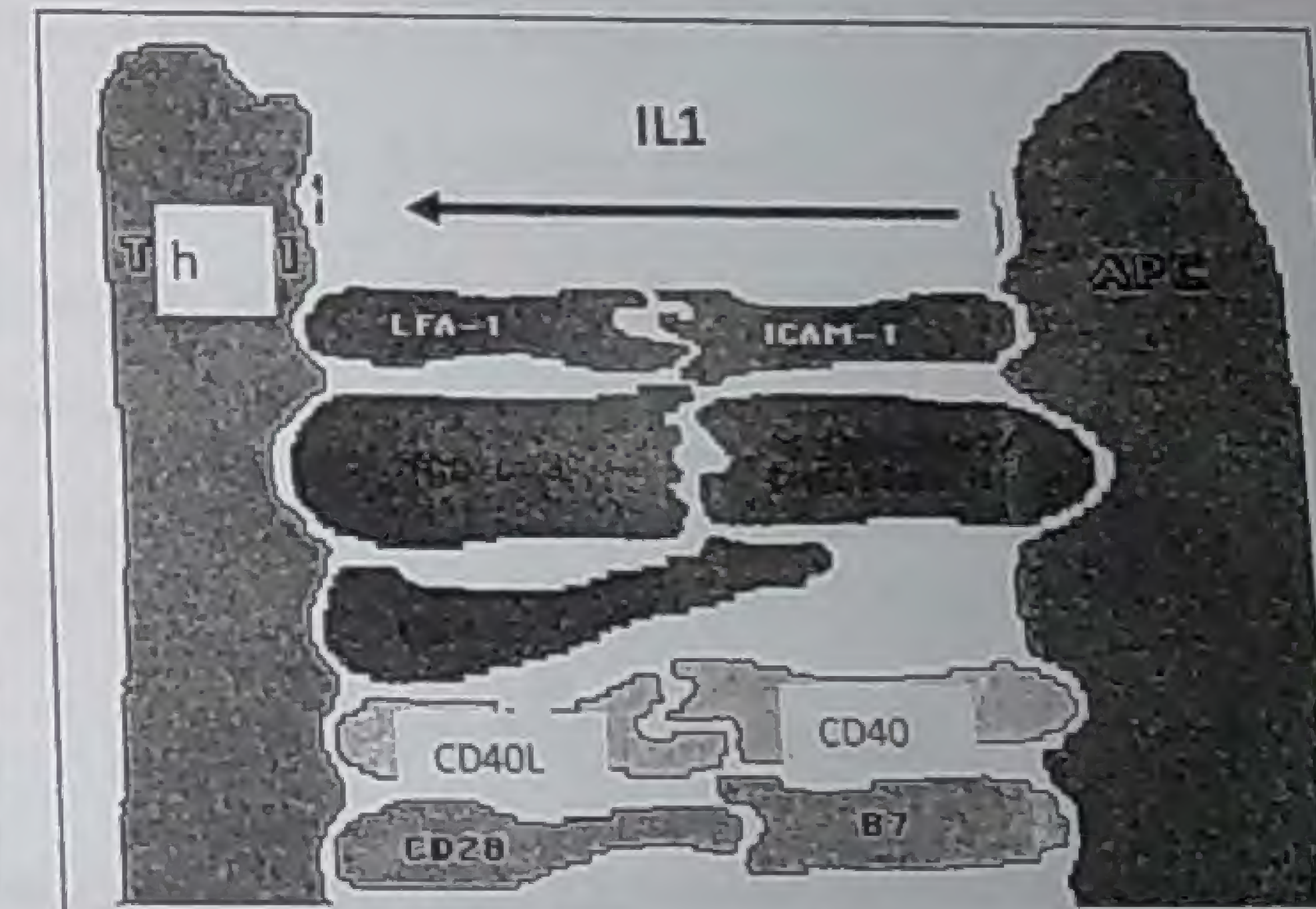
## I - Activation of naïve Th cells

### A-Recognition of Ag



### 2- Co-stimulatory molecules needed for activation

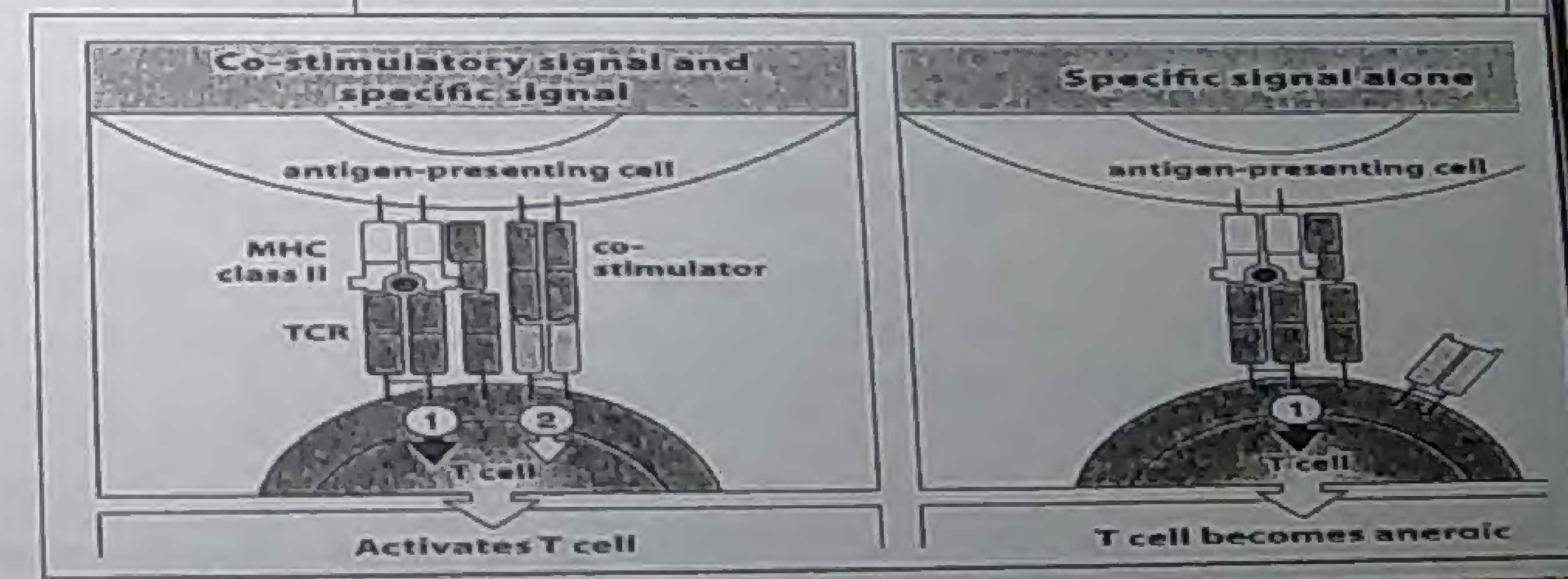
i.B7 on APCs	Interacts with	CD28 on Th cells
ii.ICAM-1 on APCs (Intercellular ad.mol.1)	Interacts with	LFA-1 on Th cells (Leuc.func.ass.Ag 1)
iii.CD40 on APCs	Interacts with	CD40L on activated Th cells
iv.IL1 from MQ & dendritic cells	Activates	Th cells



### NB Anergy

If TCR interacts with its specific Ag & *costimulatory signals don't occur*

↓  
Anergy (unresponsiveness)





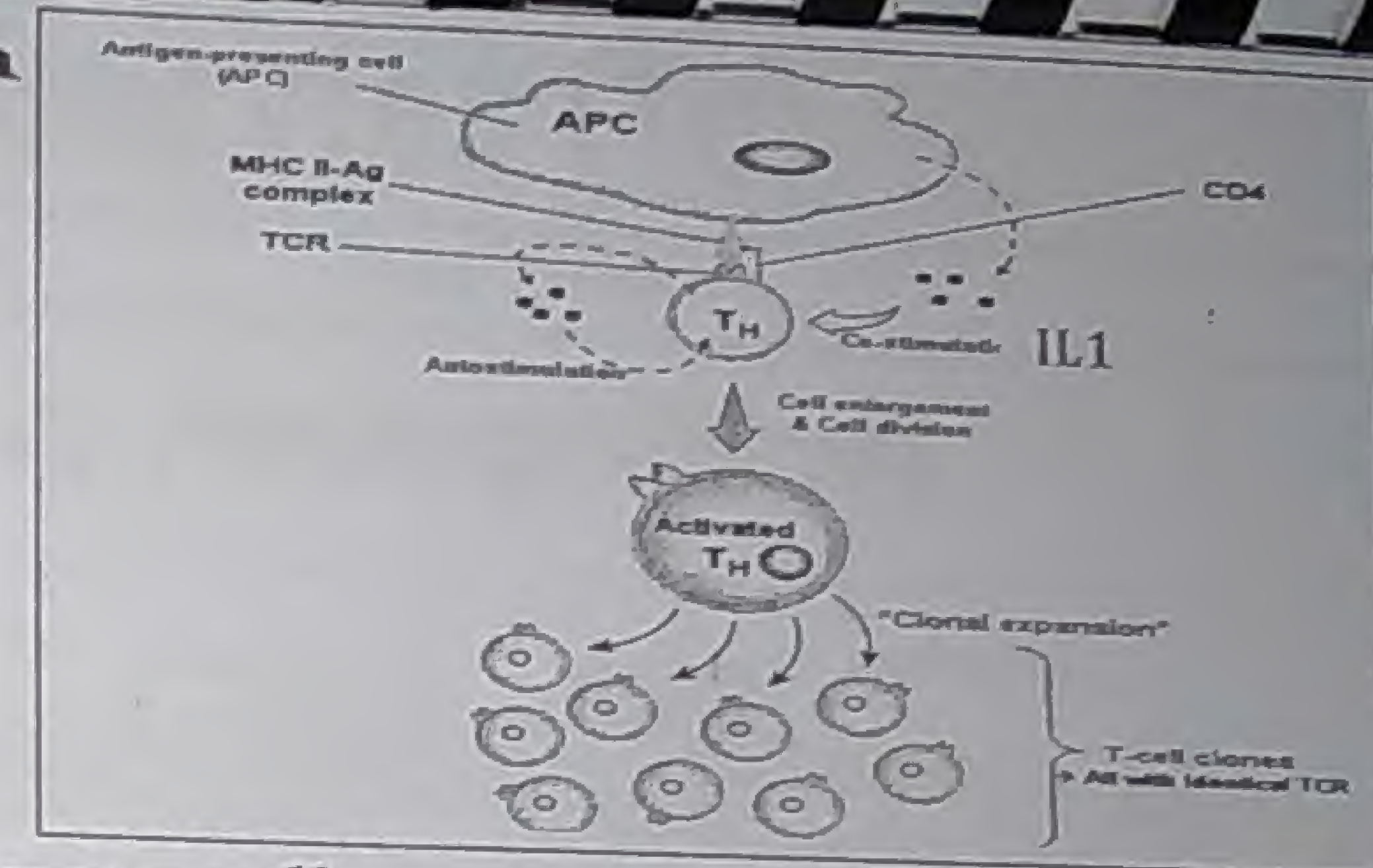
## II-Consequences of naïve Th cell activation

### A-Clonal expansion

Once activated, naïve T cell replicate

↑n= of Ag specific T cells

Cope with microbial replication



### B-Differentiation into effector cells & memory cells

Effector cells

Th1

Th2

For rapid elimination of Ags

Secrete different cytokines

Memory cells

Responds *faster & stronger*  
on encountering same Ag later in life

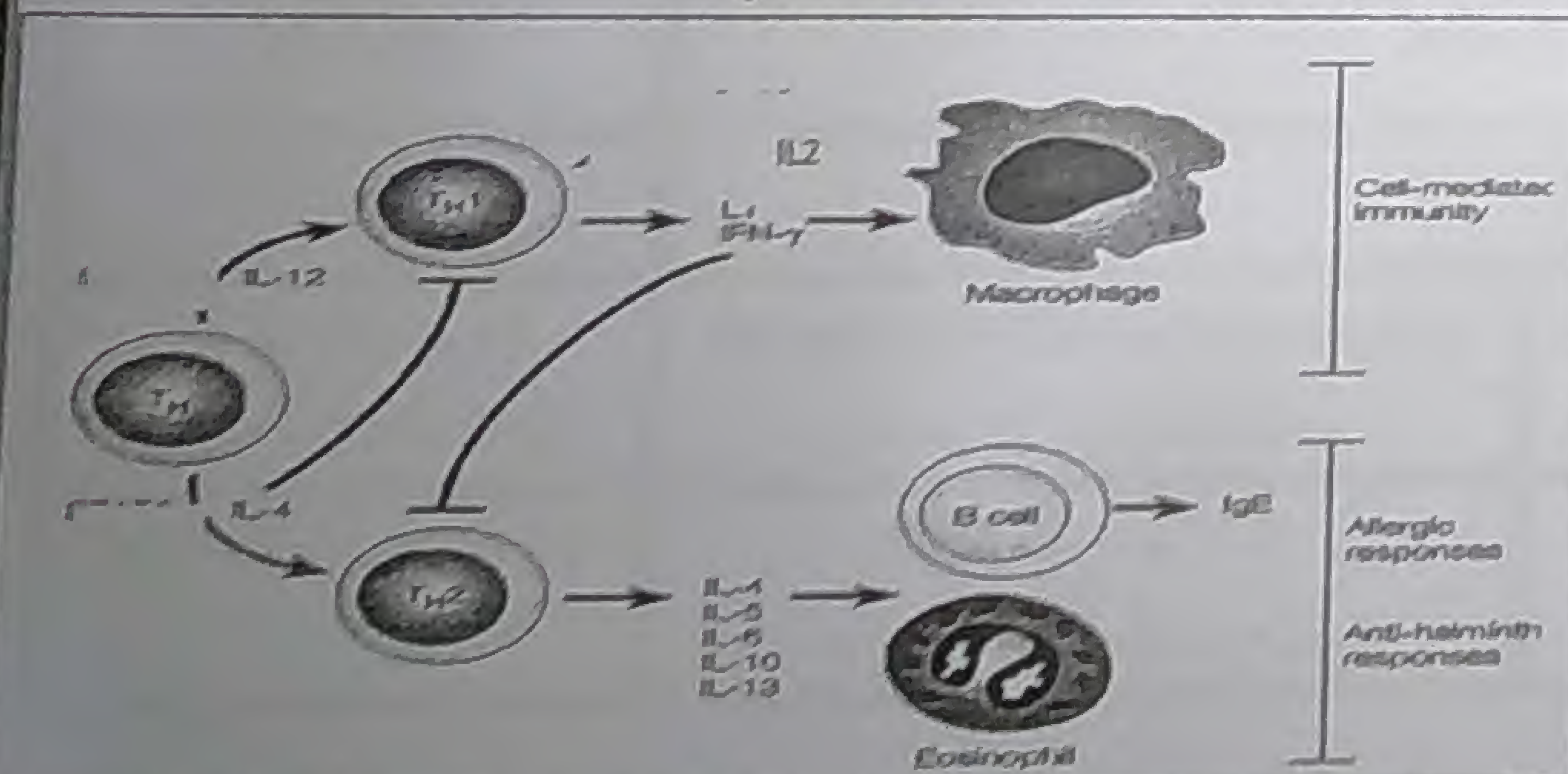
IL2 & IFN $\gamma$

⊕ MQ, NK, Tc & B cells

IL4, 5, 6, 10 & 13

⊕ B cells, eosinophils

Helminthic immunity & allergy



✓ Comparison between Naïve T cells & memory T cells

Naïve T cells	Memory T cells
1-Generated and act during 1ry IR	Generated during 1ry IR but remain <i>inactive</i> Activated in 2ry IR Faster & vigorous response on re-exposure to same Ag even eve after years
2-Require more Ag & more costimulation	Require <i>Less</i> amount of Ag & <i>less</i> costimulation
3-Produce less cytokines	Produce <i>greater amounts</i> of cytokines



# CD8+ T Cytotoxic lymphocytes (Tc)

Role of MHC class I

Activation

## Role of MHC class I in Ag recognition

Cells infected with IC pathogens :

Viruses, or IC bacteria (e.g. *Mycob. TB*)

synthesize new viral or bacterial proteins (Ags) in their cytoplasm

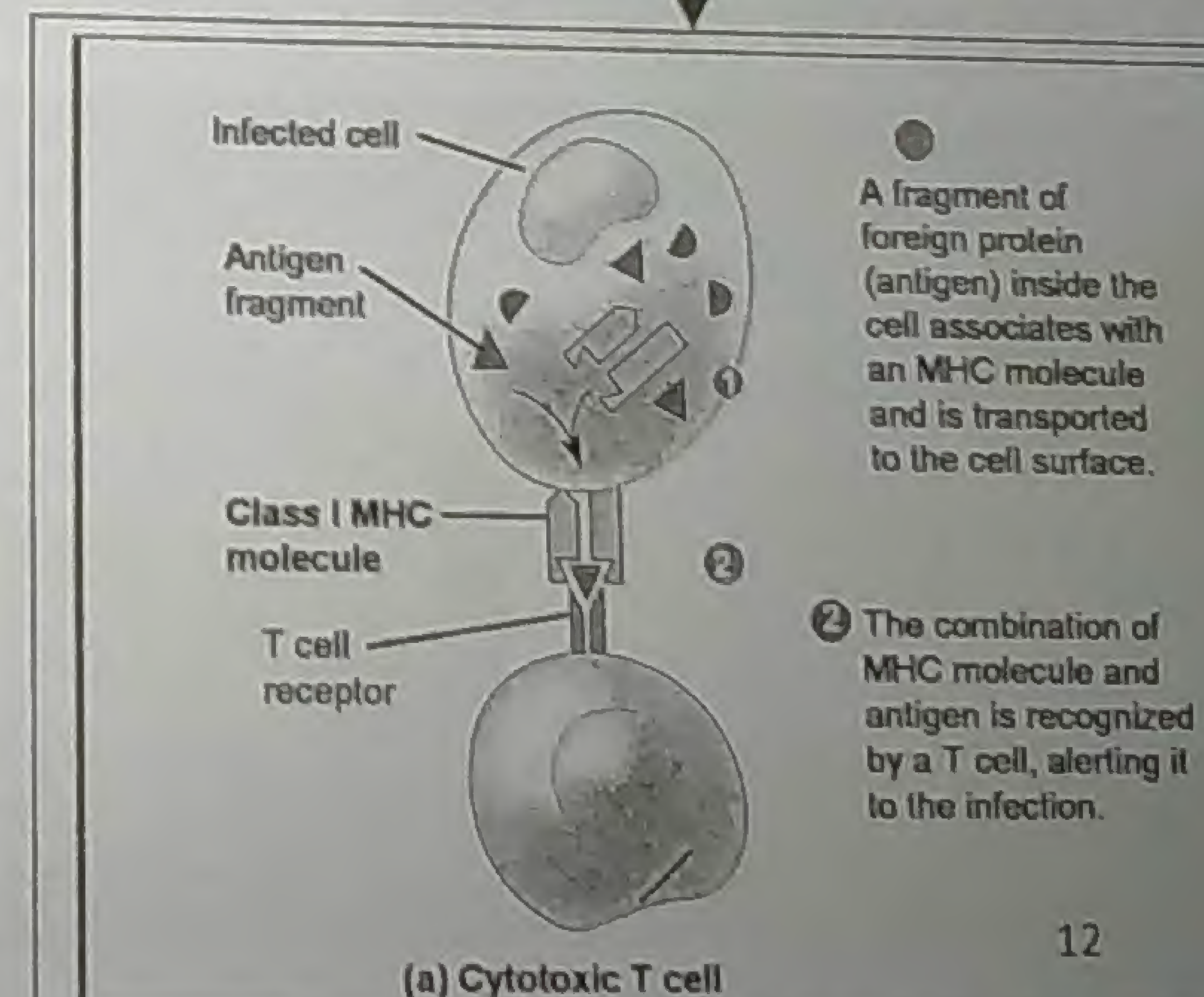
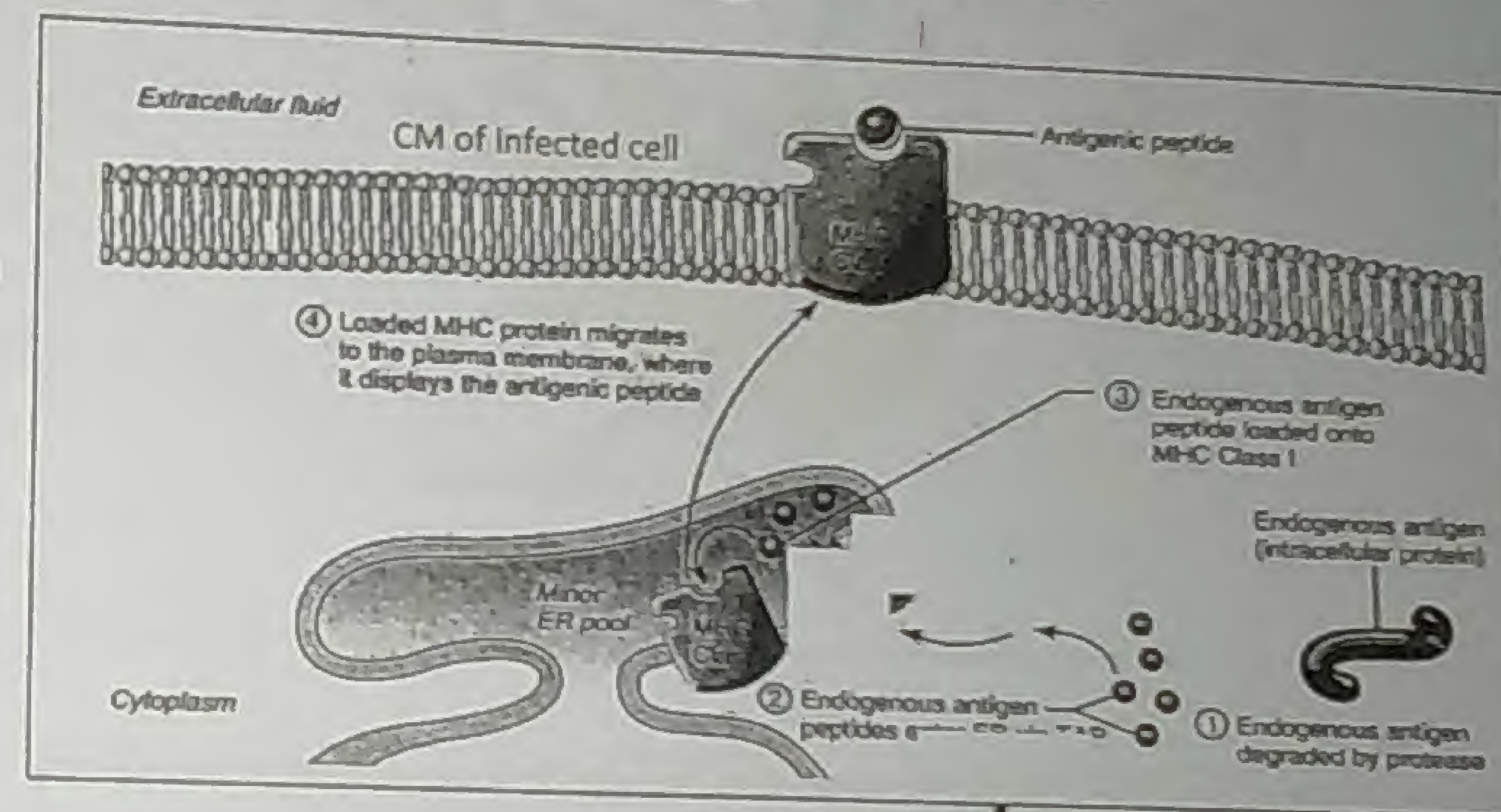
Degrade it into fragments (peptides) by enzymes

Fragments are associated with MHC class I mol.

Transported & displayed on cell surface

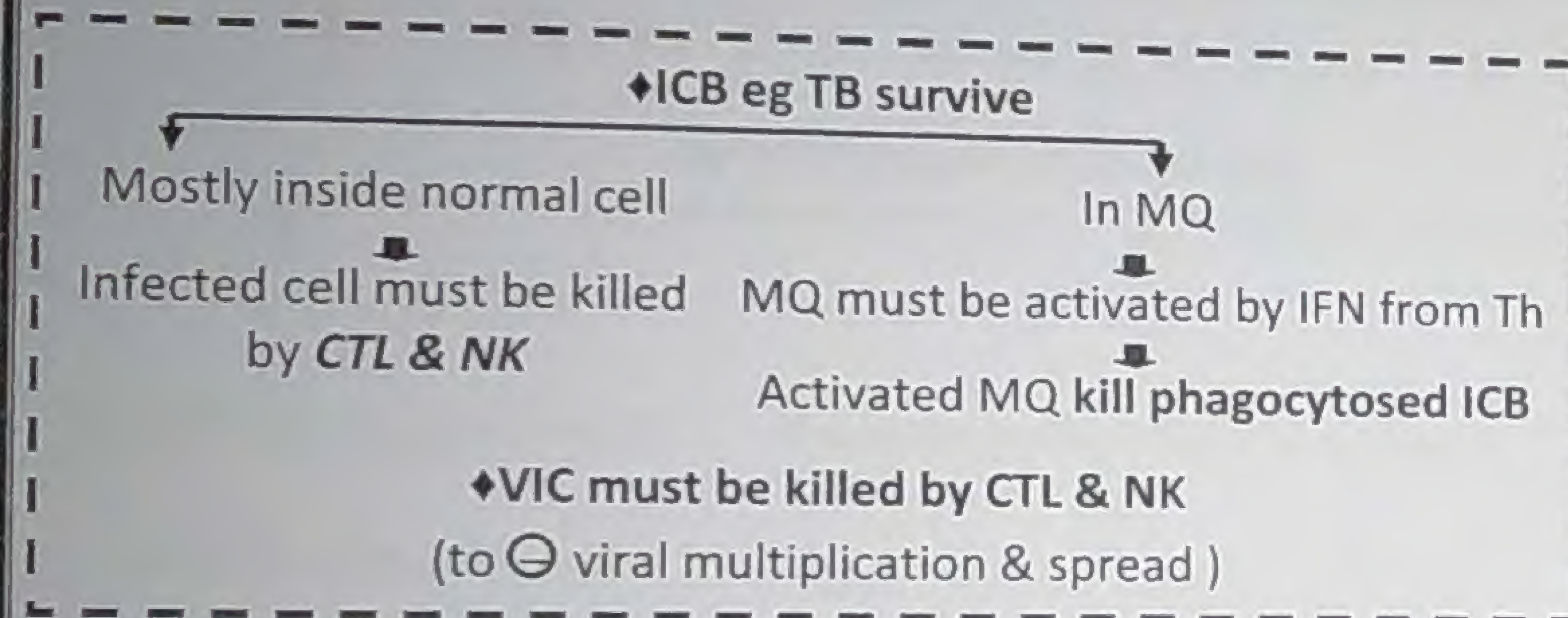
Recognized by CD8+CTLs

✓ Compare between MHC class I & II molecules



	MHC class I	MHC class II
1-Site	Mention	
2-Structure	Mention	
3-Source of expressed Ag	Newly synthesized proteins from IC pathogens	Fragments of phagocytosed particles
4-Recognized by	CD8 mol & TCR on Tc lymphocytes	CD4 mol & TCR on Th lymph





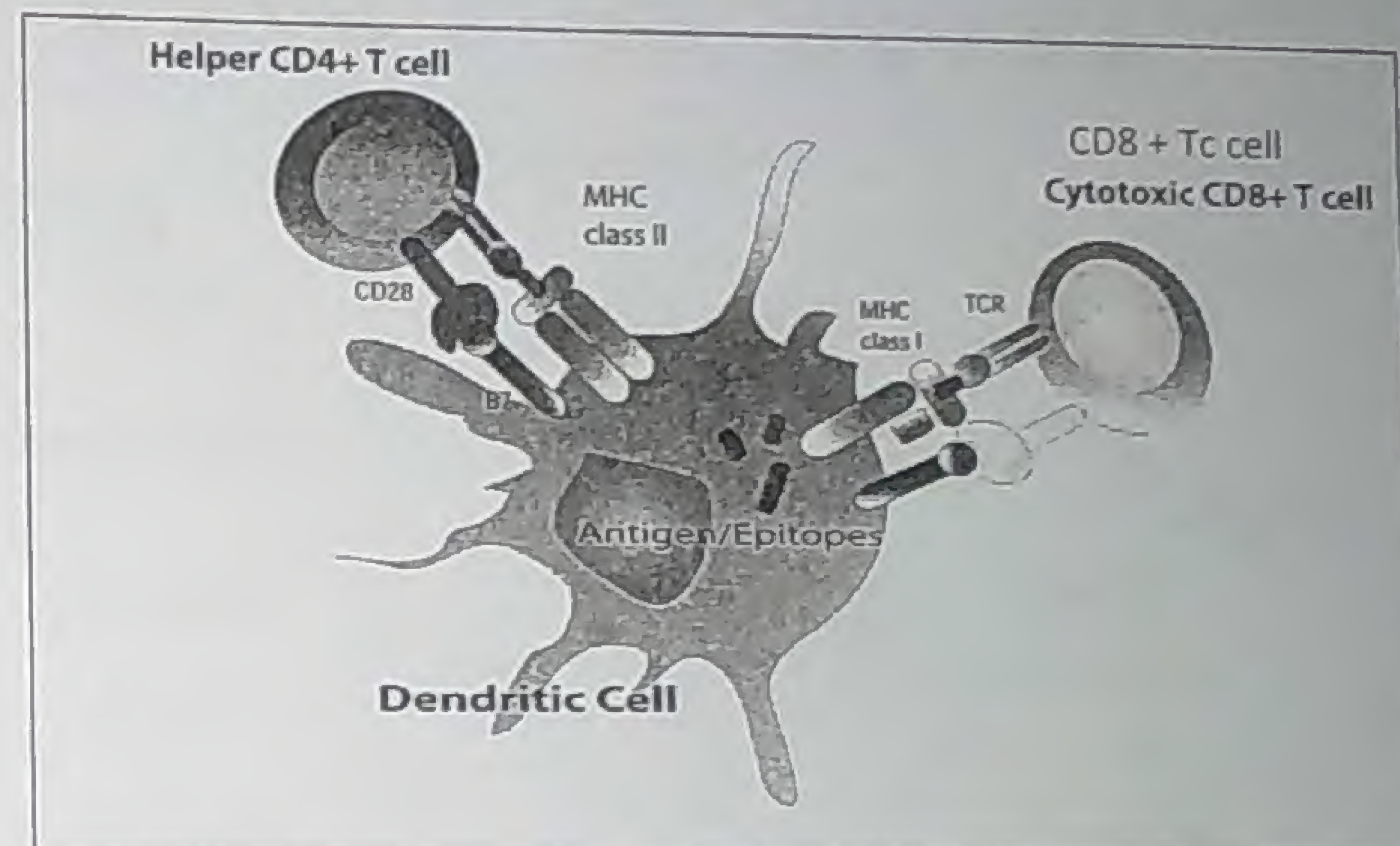
In case of IC pathogens, APCs present Ag with **both MHC class II & I**

⊕ **both Th & Tc.**

In case of EC pathogens, APCs present Ag with MHC class II only

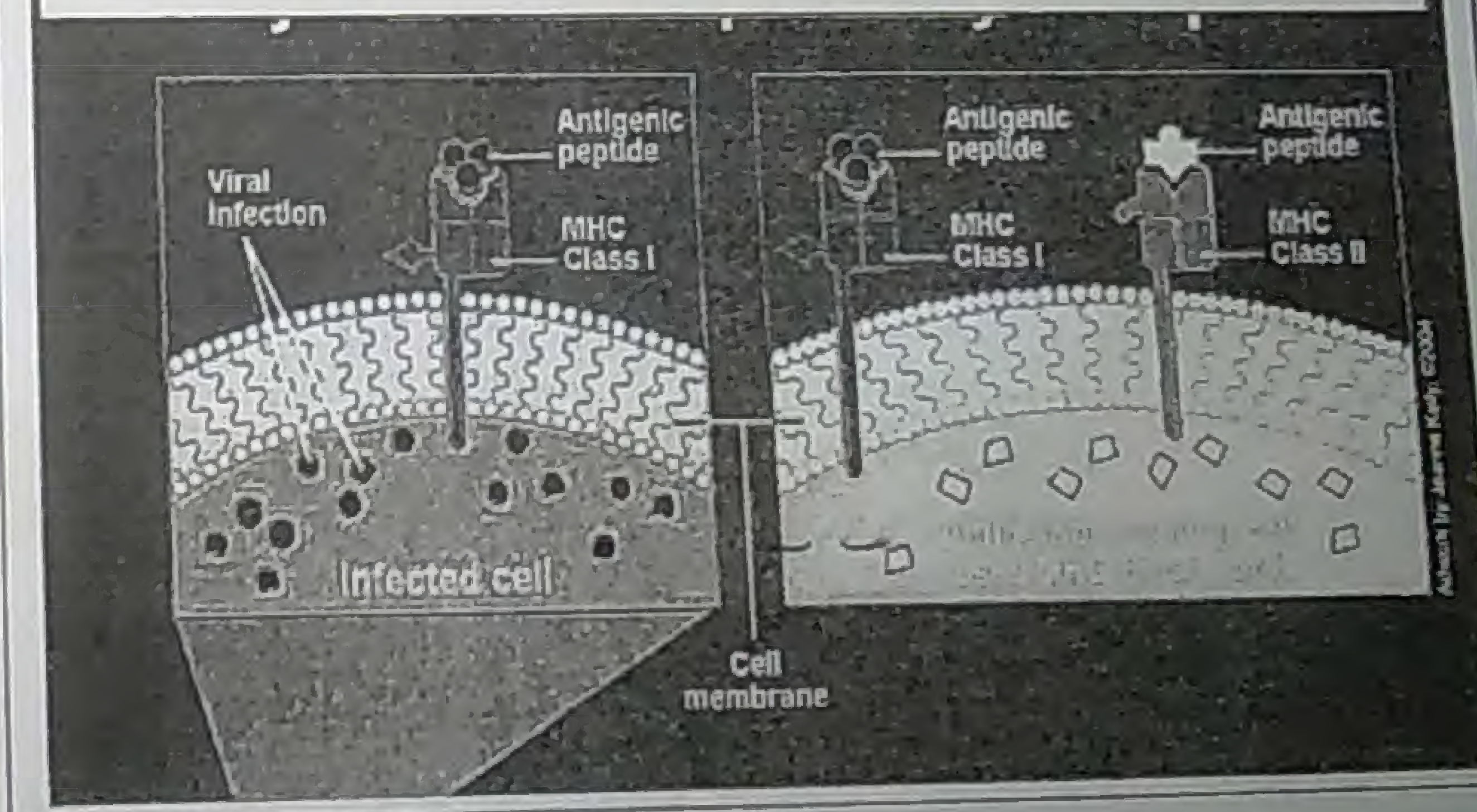
⊕ **Th only**

ECB (most of bacteria) : live mostly outside the cell



VIC

APC ingesting virus

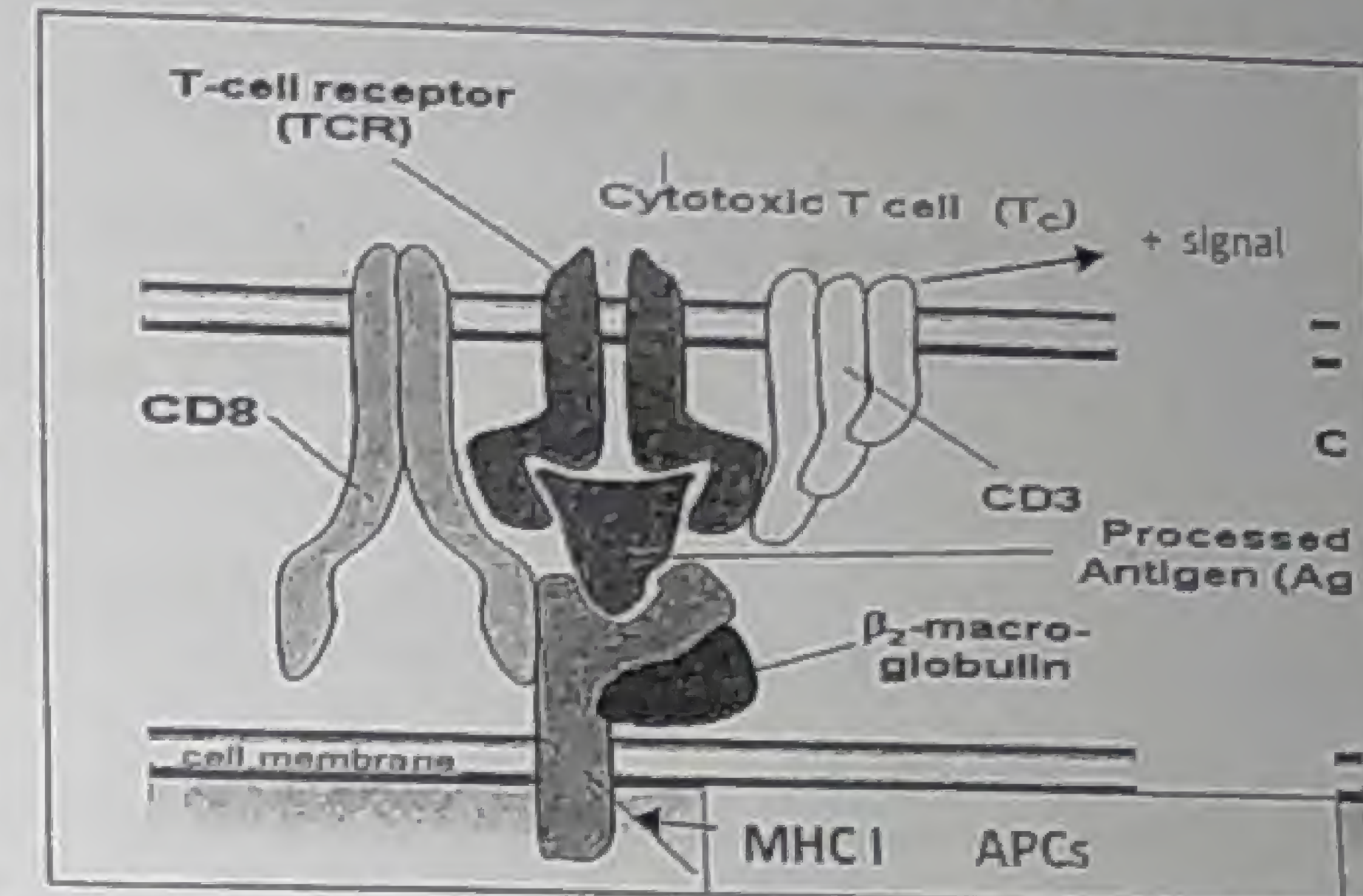
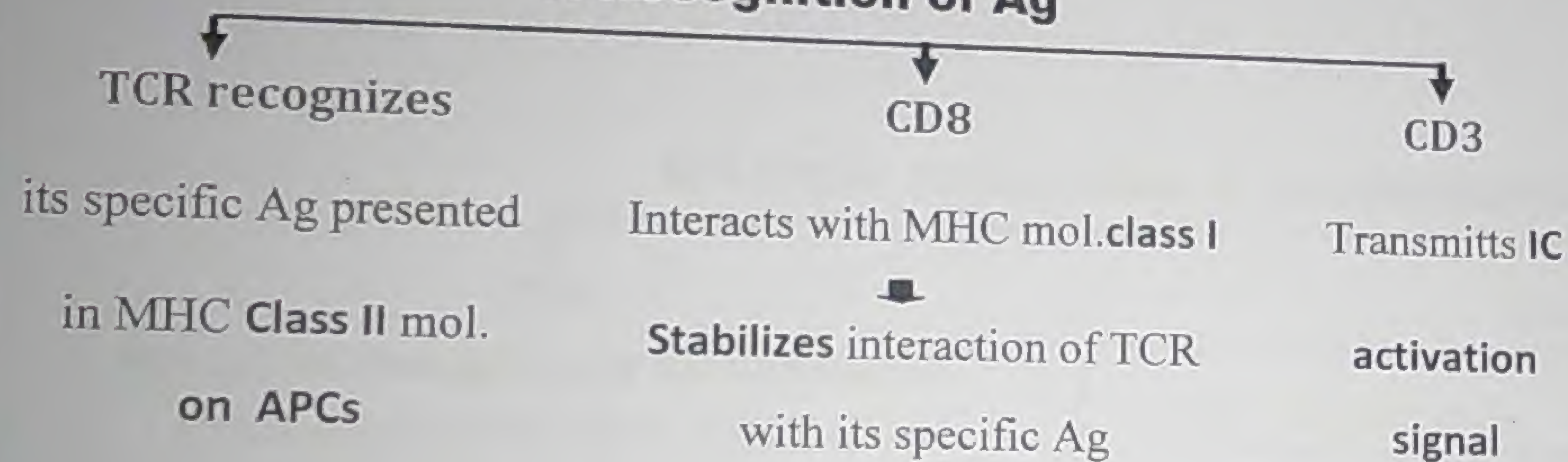




# Activation of CD8 Tc cells

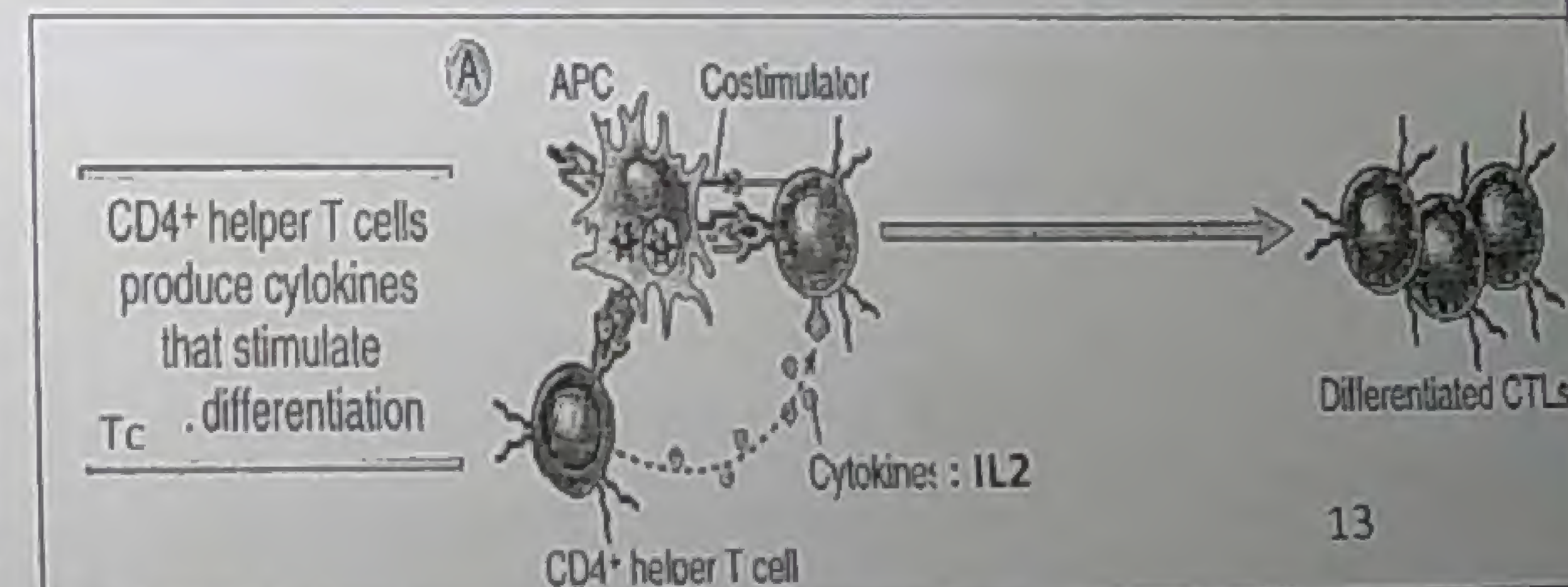
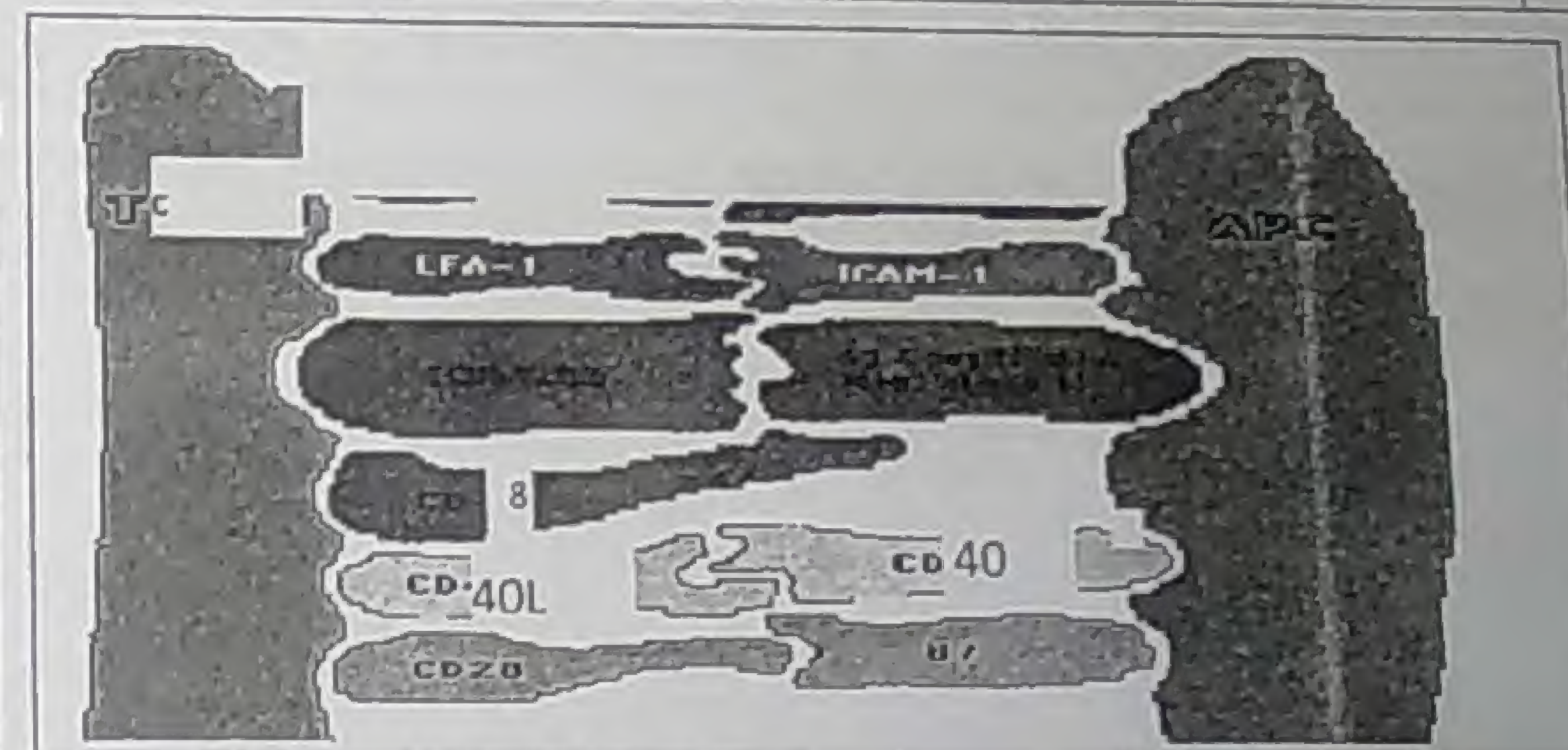
## I - Activation of naïve Tc cells

### A-Recognition of Ag



### B- Co-stimulatory molecules needed for activation

i.B7 on APCs	Interacts with	CD28 on Tc cells
ii.ICAM-1 on APCs	Interacts with	LFA-1 on Tc cells
iii.CD40 on APCs	Interacts with	CD40L on activated Tc cells
iv.IL2 from Th1	Activates	Tc cells





**C-Activated Tc replicates & differentiates into**

Effector CTLs

Memory cells

Responds *faster & stronger*

on encountering same Ag later in life

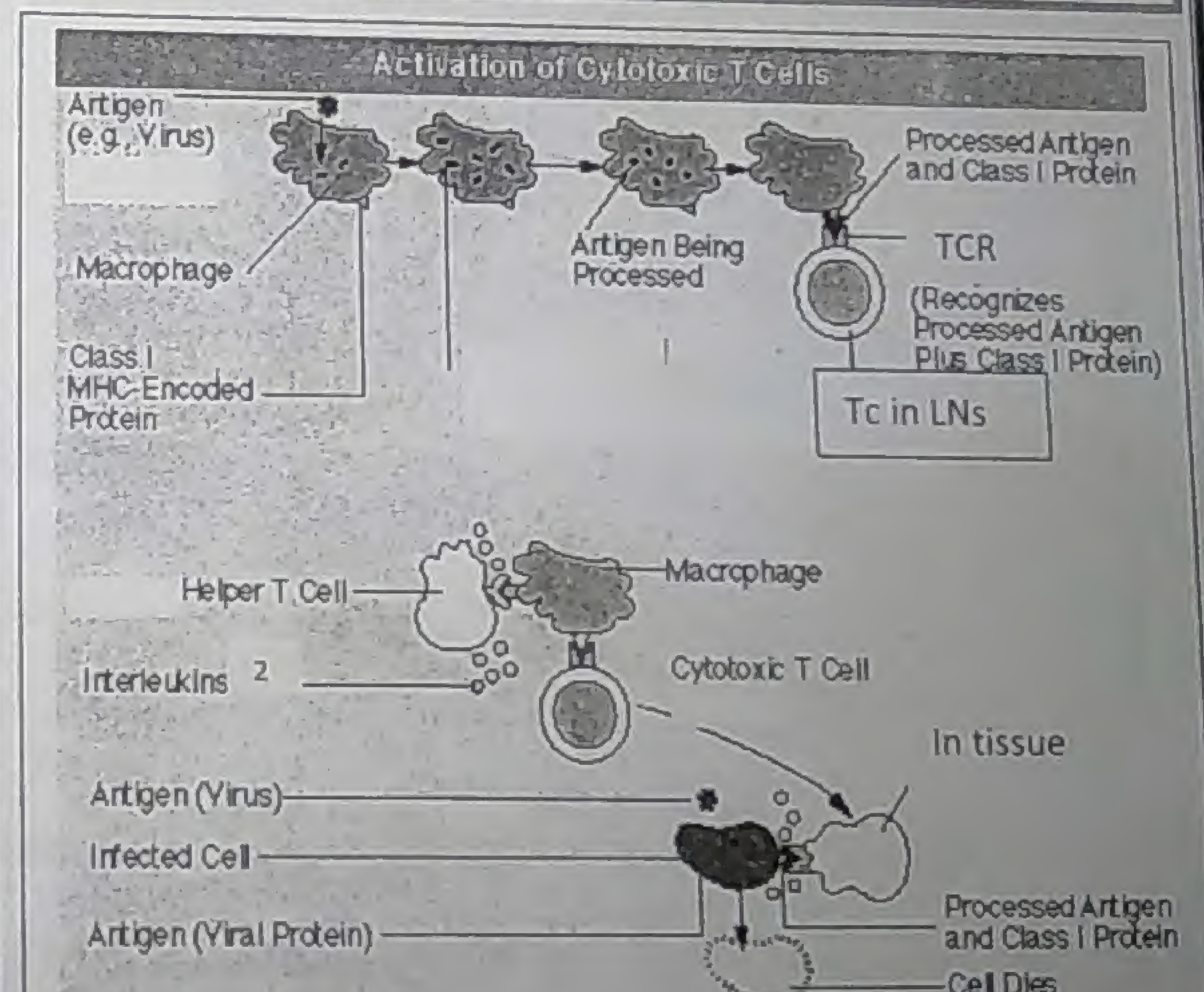
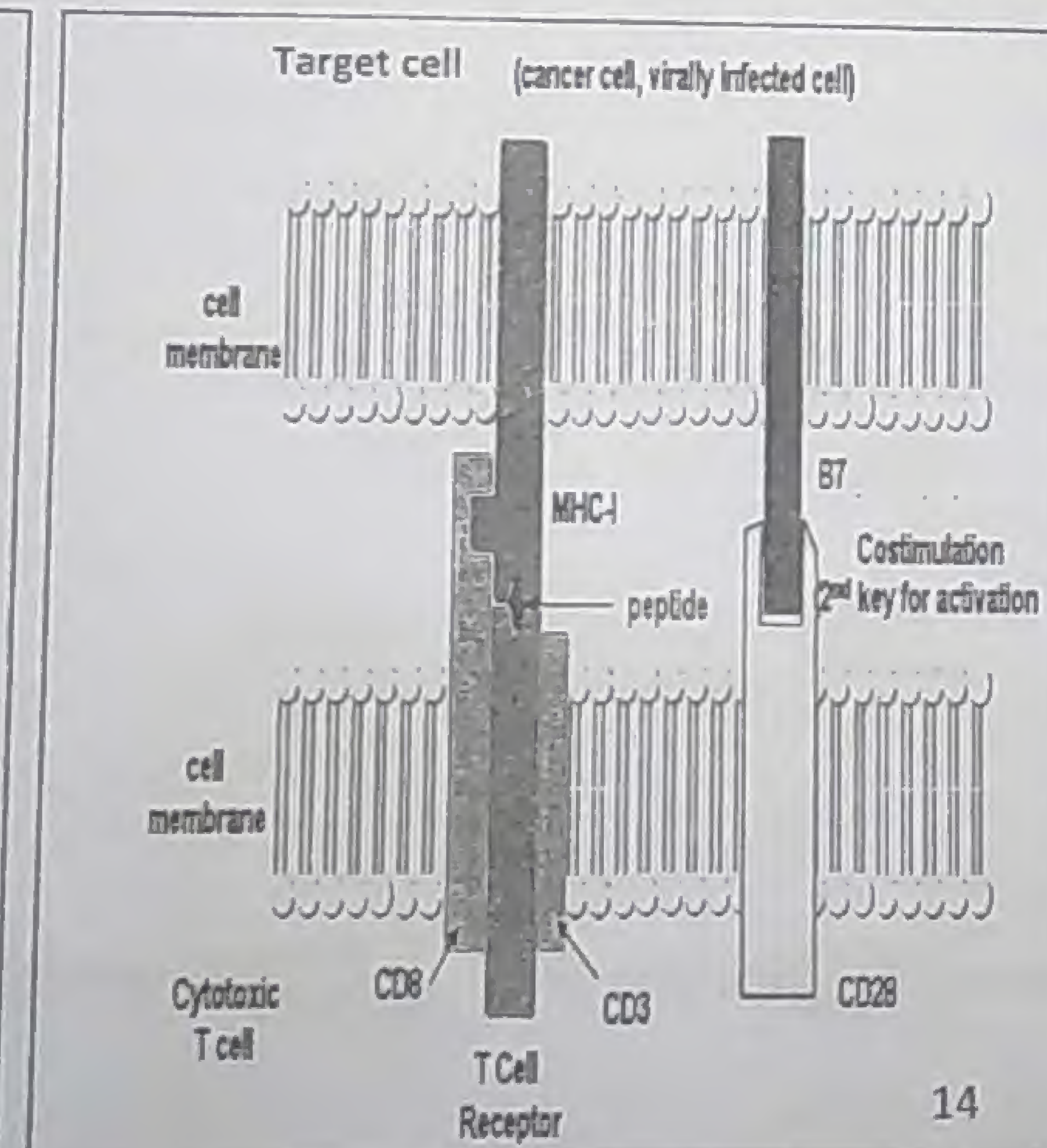
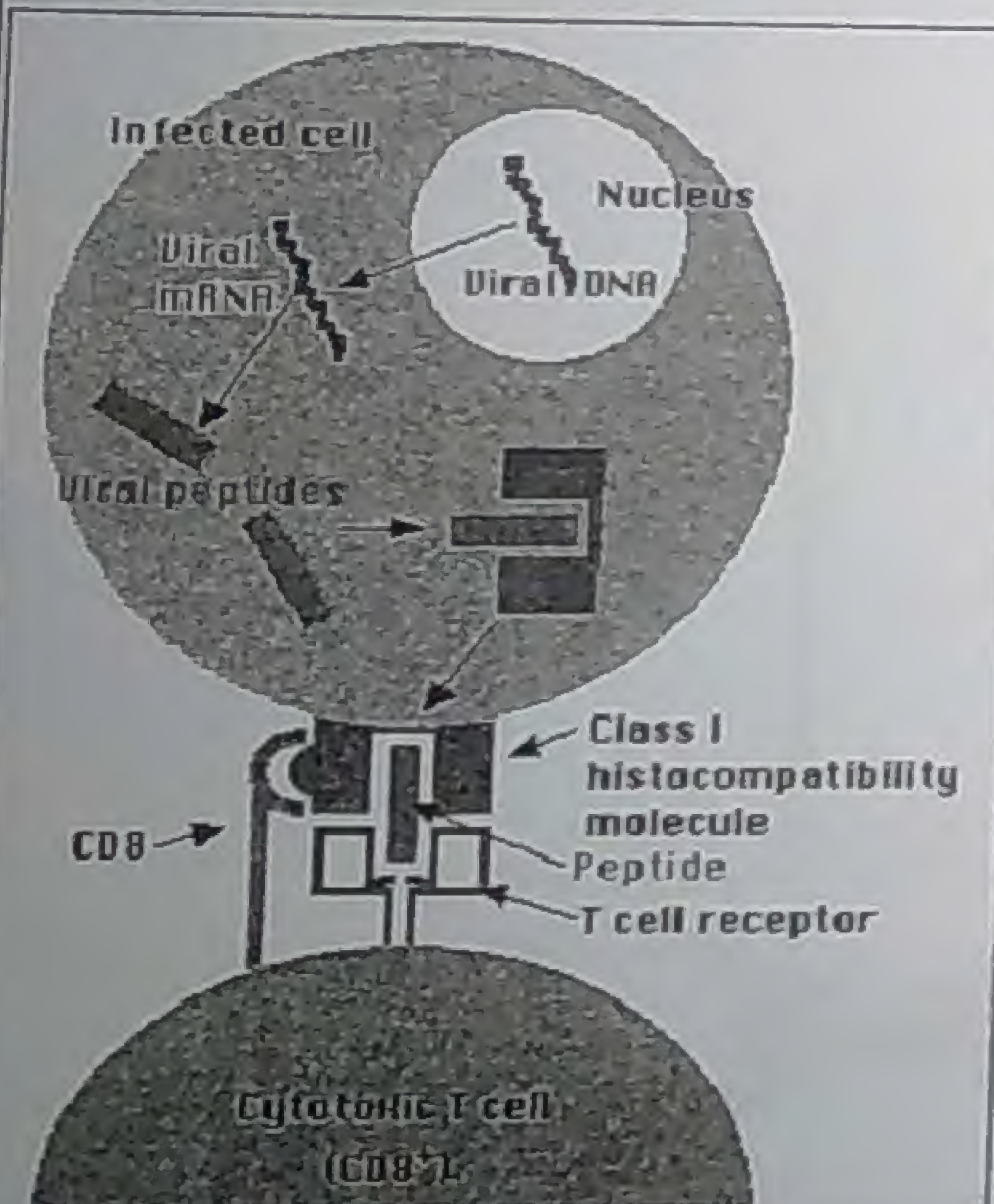
**D-Target recognition & costimulation of CTLs**

TCR

Costimulatory molecules

recognizes **endogenously synthesized Ag**  
in association with MHC class I mol  
on the surface of **target cells**

i.B7 on target cells	Interacts with	CD28 on CTLs
ii.ICAM-1 on target cells	Interacts with	LFA-1 on CTLs





## II-Killing of target cells by effector CTLs (EC killing or cytotoxicity)

❖ Occurs by apoptosis by one of 2 ways

### Perforin pathway

On binding to target, CTL granules fuse with its CM  
 Release of *perforins* & *granzymes* into intercellular space

Perforins form **pores** in target cell

Granzymes **enter** the cell

**Apoptosis**

### CD95 or Fas-FasL pathway

Activated CTL expresses FasL protein( CD 95L)

Binds with *Fas protein on target*

(Transmembrane receptor or CD95)

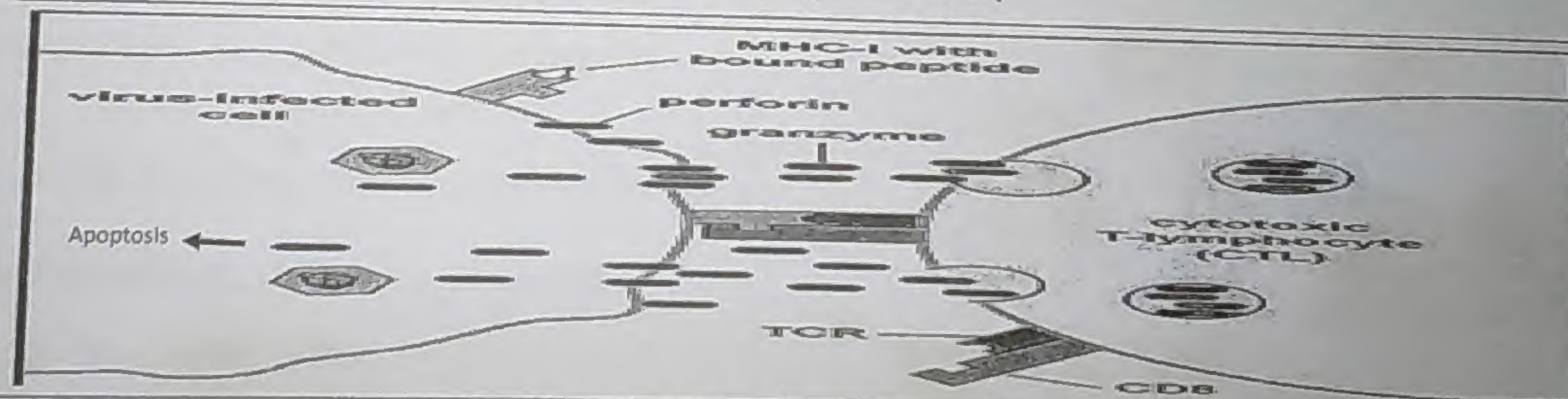
**Apoptosis**

❖ Killed target cell is phagocytosed & destroyed by surrounding MQ

Destruction of any microbe (e.g virus) inside it

NB. CTLs secrete *small amount of IL2 & IFN $\gamma$*

Perforin pathway



Fas/FasL-mediated cell killing



FasL on CTL interacts with Fas on target cell

**Apoptosis of target cell**



# Natural killer (NK) cells

## A-Characters

Size: Large granular lymphocytes  
 Maturation: BM  
 Markers:  $\blacklozenge$  CD16  $\blacklozenge$  CD56

## B-Functions

### 1-Direct EC killing (cytotoxicity)

#### i.Importance

Destroy *large* particles that *can't phagocytosed* by phagocytic cells

e.g VICs, cells with IC bacteria & tumor cells

#### ii.Target recognition: recognize cells that

Express

altered

self

molecules

*foreign antigens without MHC*

Don't express some self molecules MHC I

Some VICs, cells with ICB & tumor cells have *absent or*  $\downarrow$  *MHC class I expression* as a mechanism of survival

Release NK from a normal state of inhibition

#### iii.Mechanism of killing: *perforin* pathway (M)

### 2- Secrete IFN $\gamma$

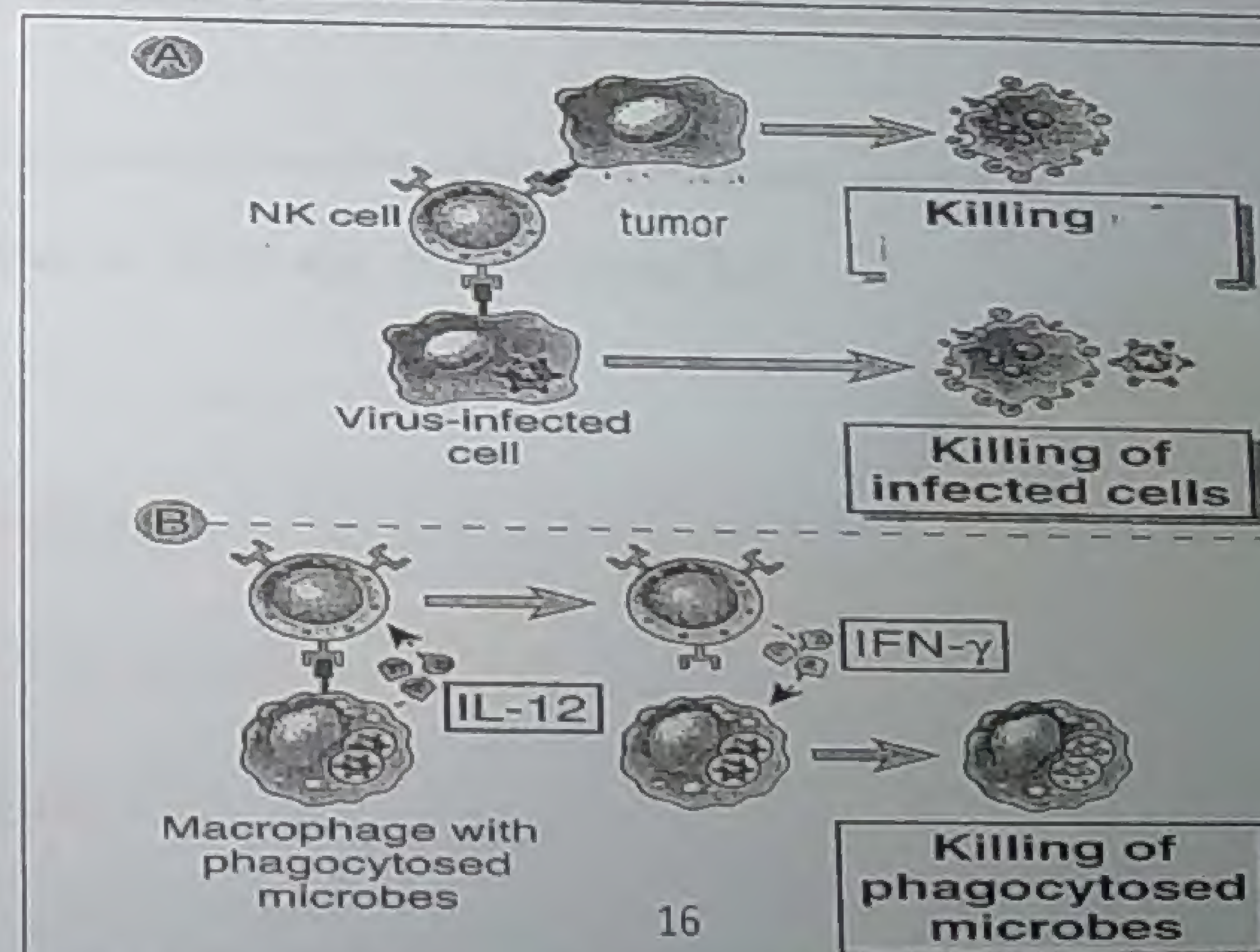
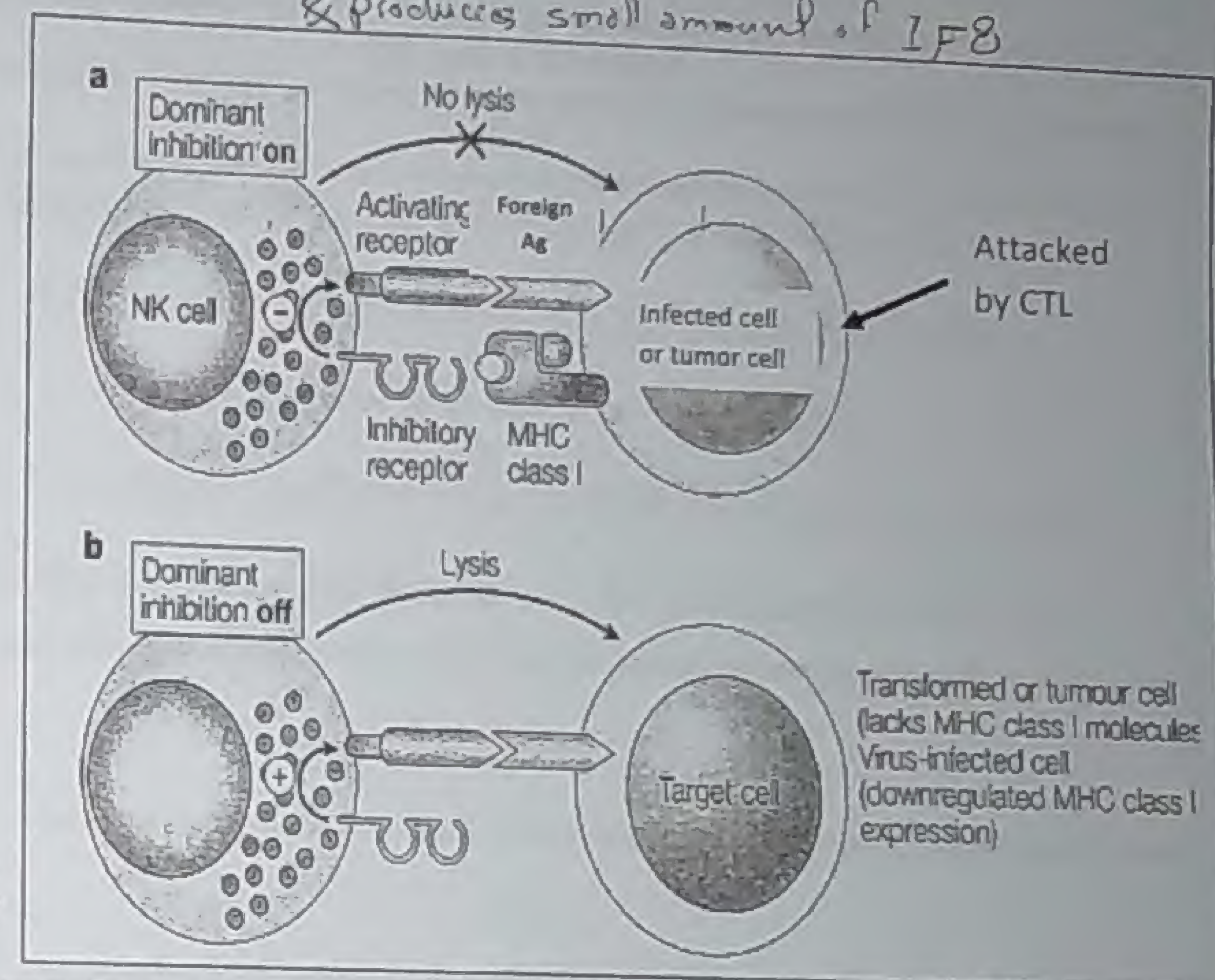
Activates MQ to kill phagocytosed IC pathogens

## C - Stimulated by

IL12 from MQ

IL2 & IFN $\gamma$  from Th1 & CTL

*& produces small amount of IF8*





## Differences between Tc & NK cells

	<b>Tc</b>	<b>NK cells</b>
1-Maturation	Thymus	BM
2-Target recognition	i. Ag specific : by TCR ii. Recognizes target expressing MHC class I + foreign Ag	i. <i>Not specific</i> : recognize cells expressing altered molecules ii. <i>Absence of MHC class I releases NK cells</i> from a normal state of inhibition NK recognize cells in which ICB or viruses or tumor ↓ <i>MHC class I expression</i> as mechanism of survival
3-Mechanism of killing	CD95 or Fas-FasL pathway	No
4-IL2 production	Yes	No
5-Memory cells	Yes	No

## Common features between Tc & NK cells

1- Targets : VICs , Cells with ICB & tumor cells

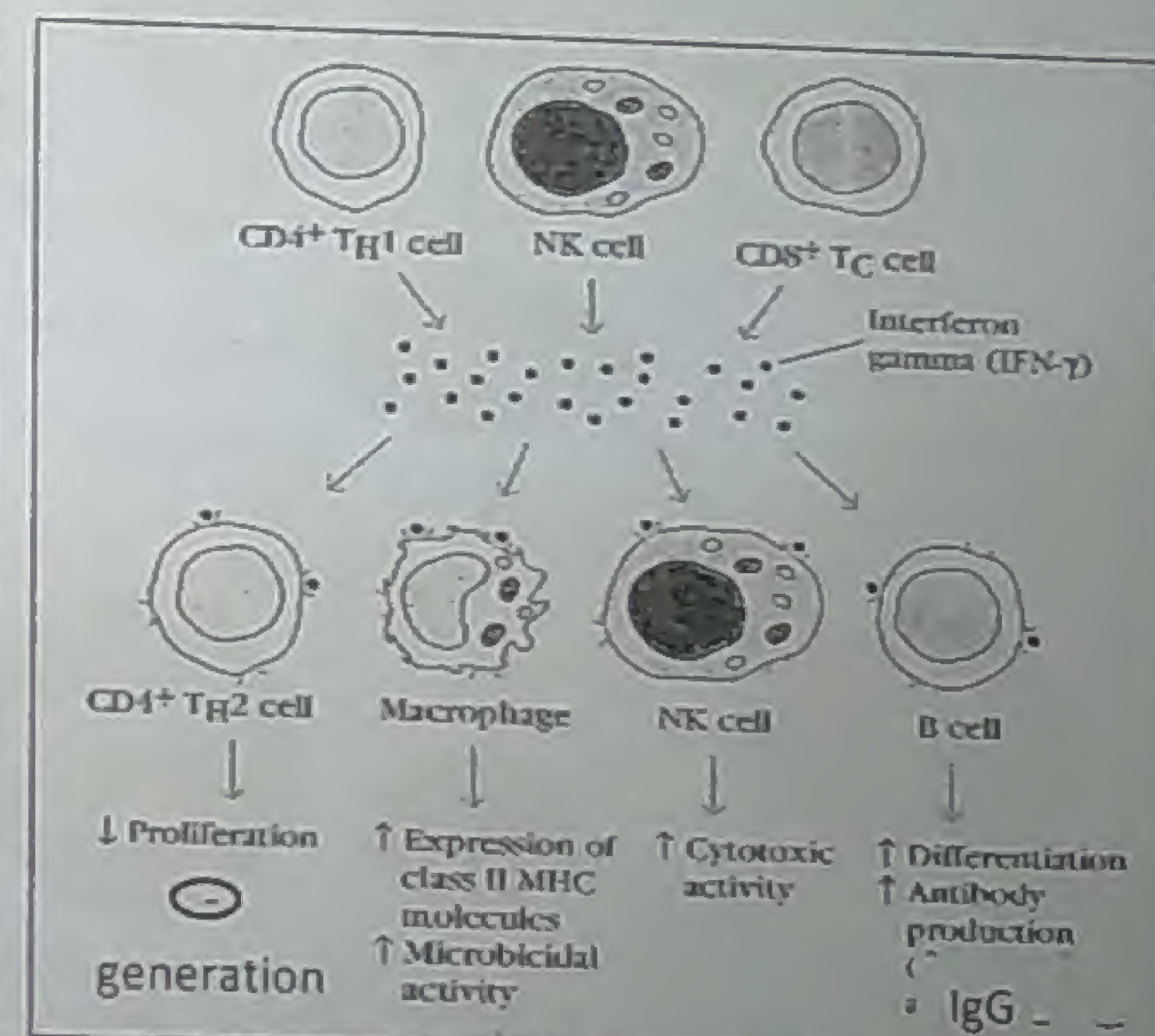
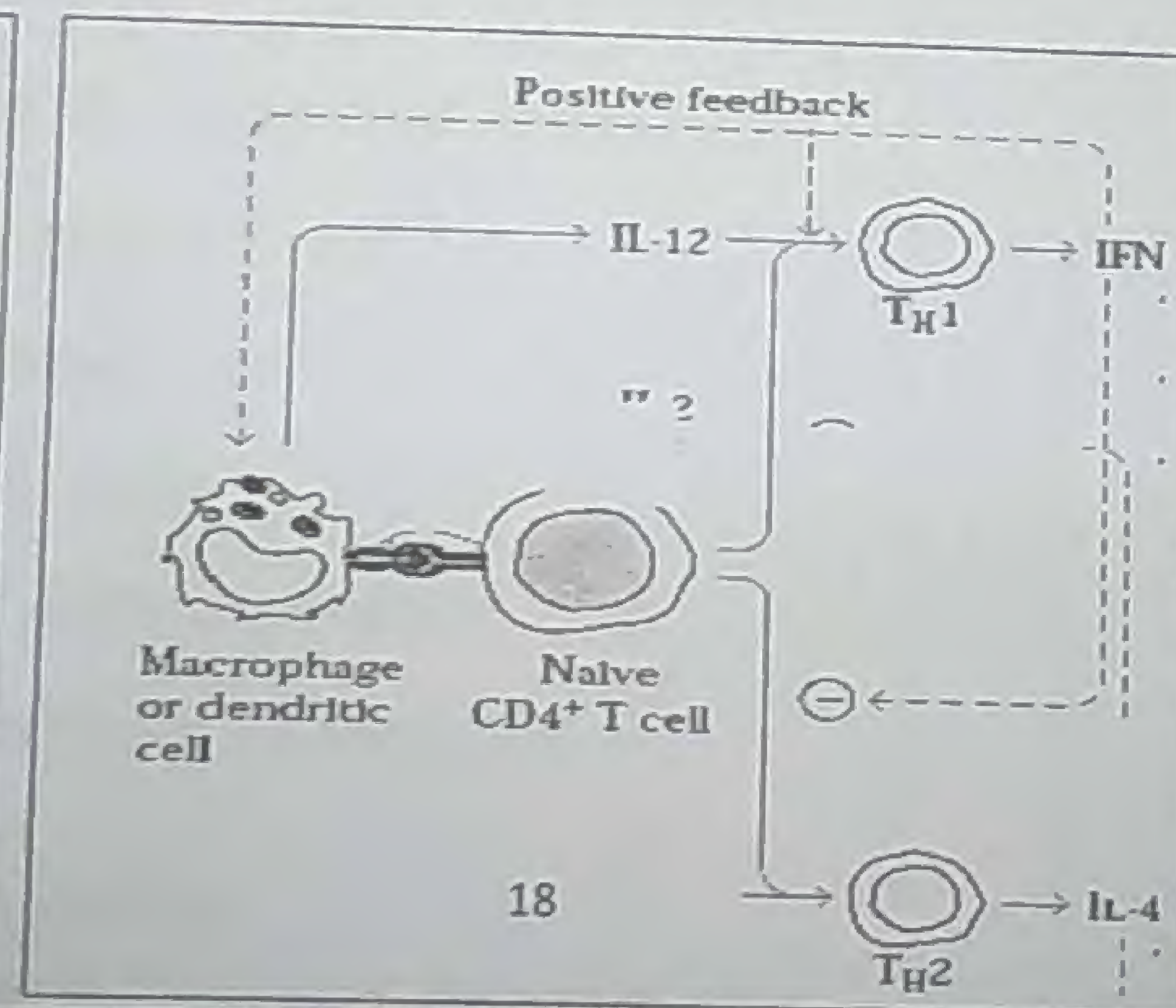
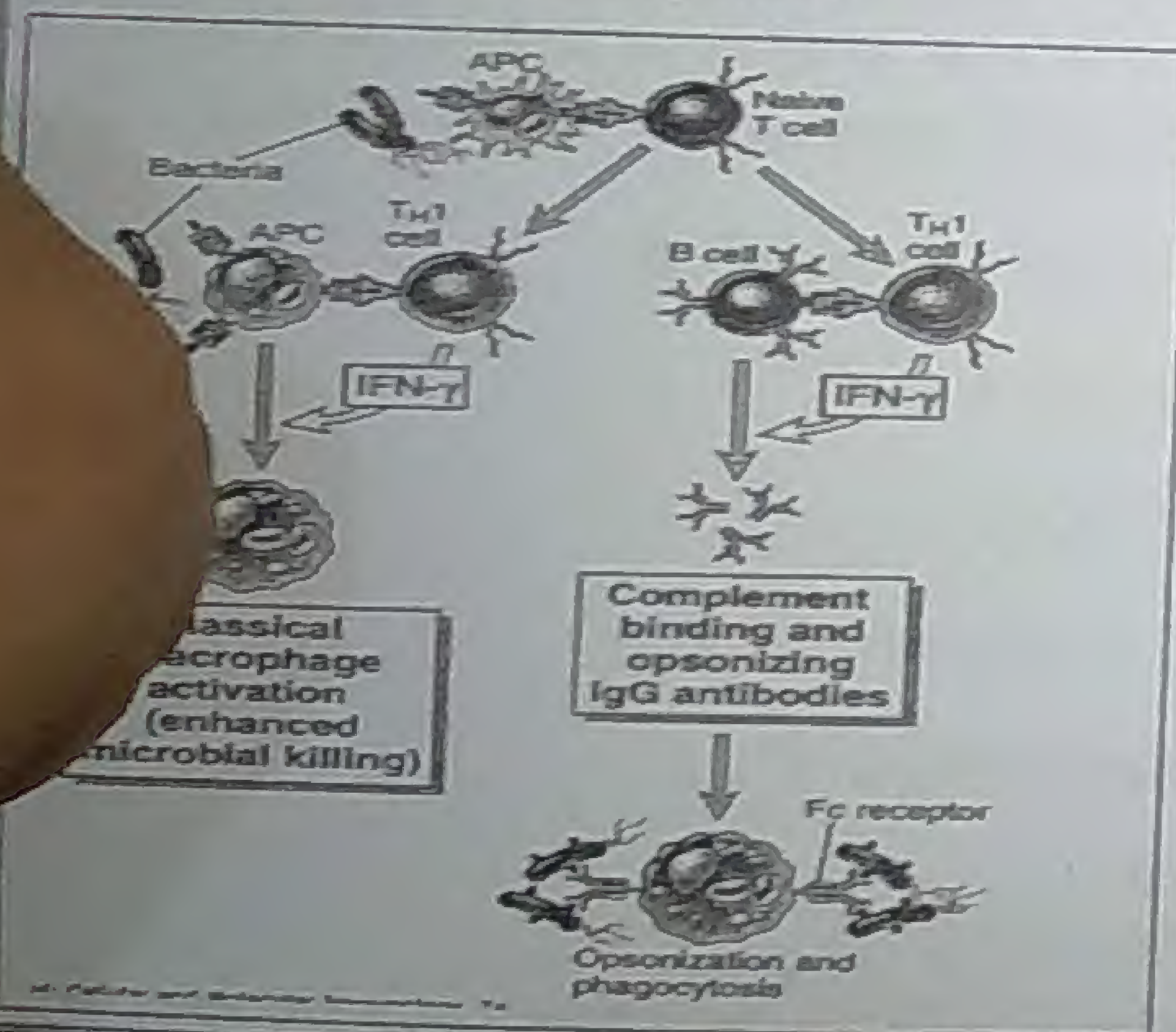
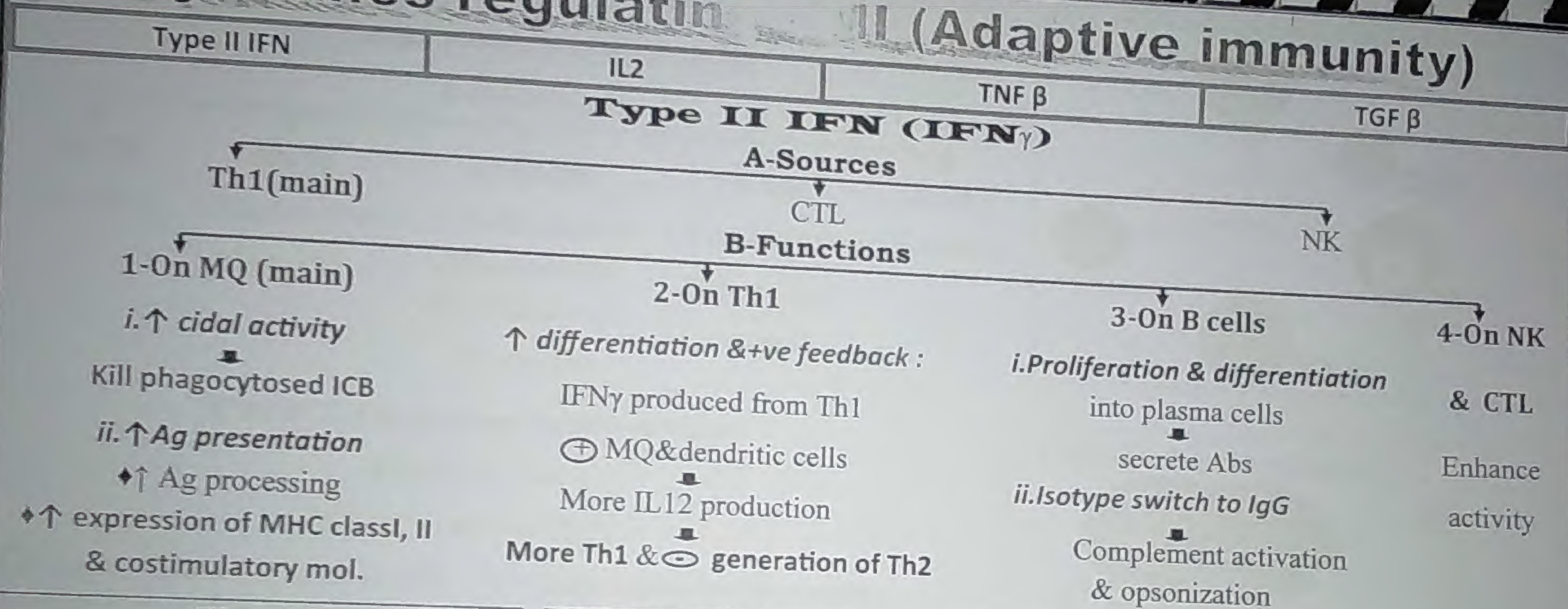
2- Kill by **perforin** pathway.

3- Produce IFN $\gamma$  which  $\oplus$  MQ to kill phagocytosed IC org.

4- Stimulated by IL2 from Th1



# Cytokines regulation II (Adaptive immunity)

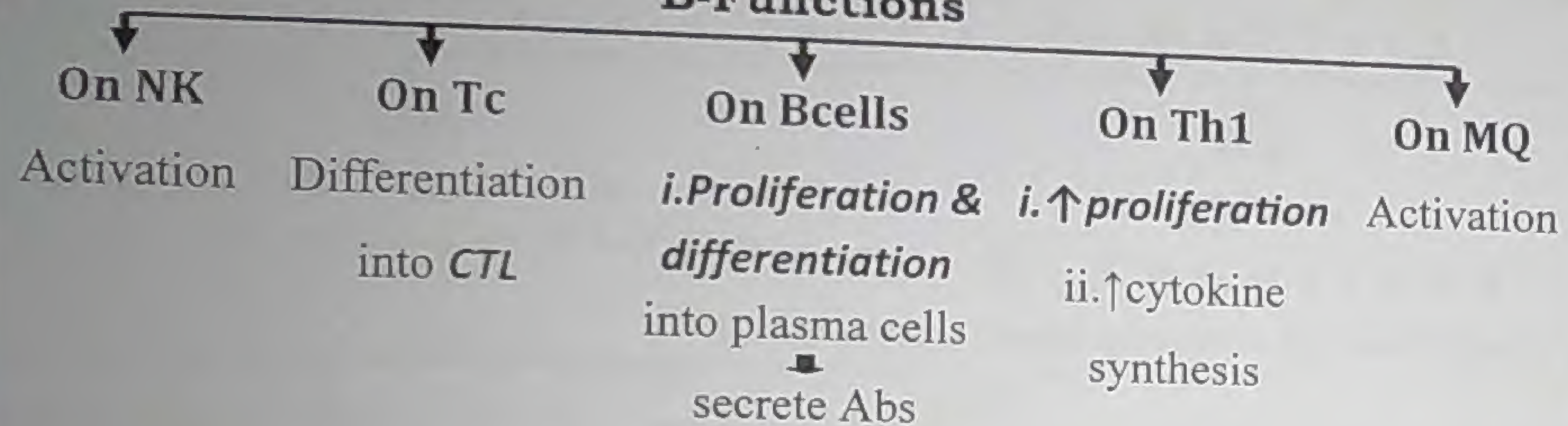




## IL2

**A-Sources :** Th1(main) & CTL

### B-Functions



## TNF $\beta$ (Lymphotoxin)

**A-Source :** Th1

**B-Functions :** as TNF $\alpha$

⊕ neutrophils & endothelial cells → Coagulation & inflammation

## IL12 : Link between innate & adaptive immunity

**A-Source :** MQ & dendritic cells

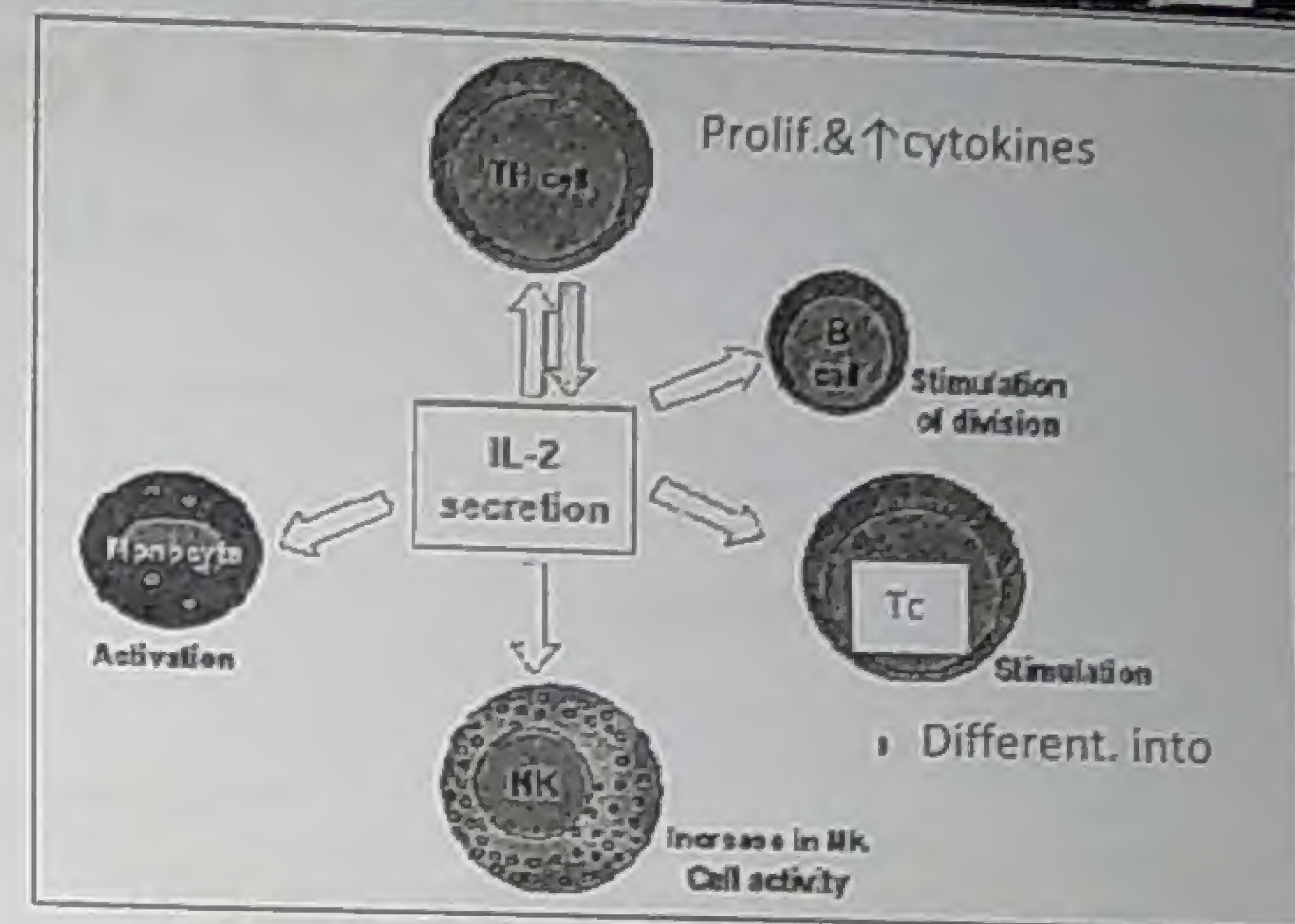
### B-Functions

1- ⊕ NK cells

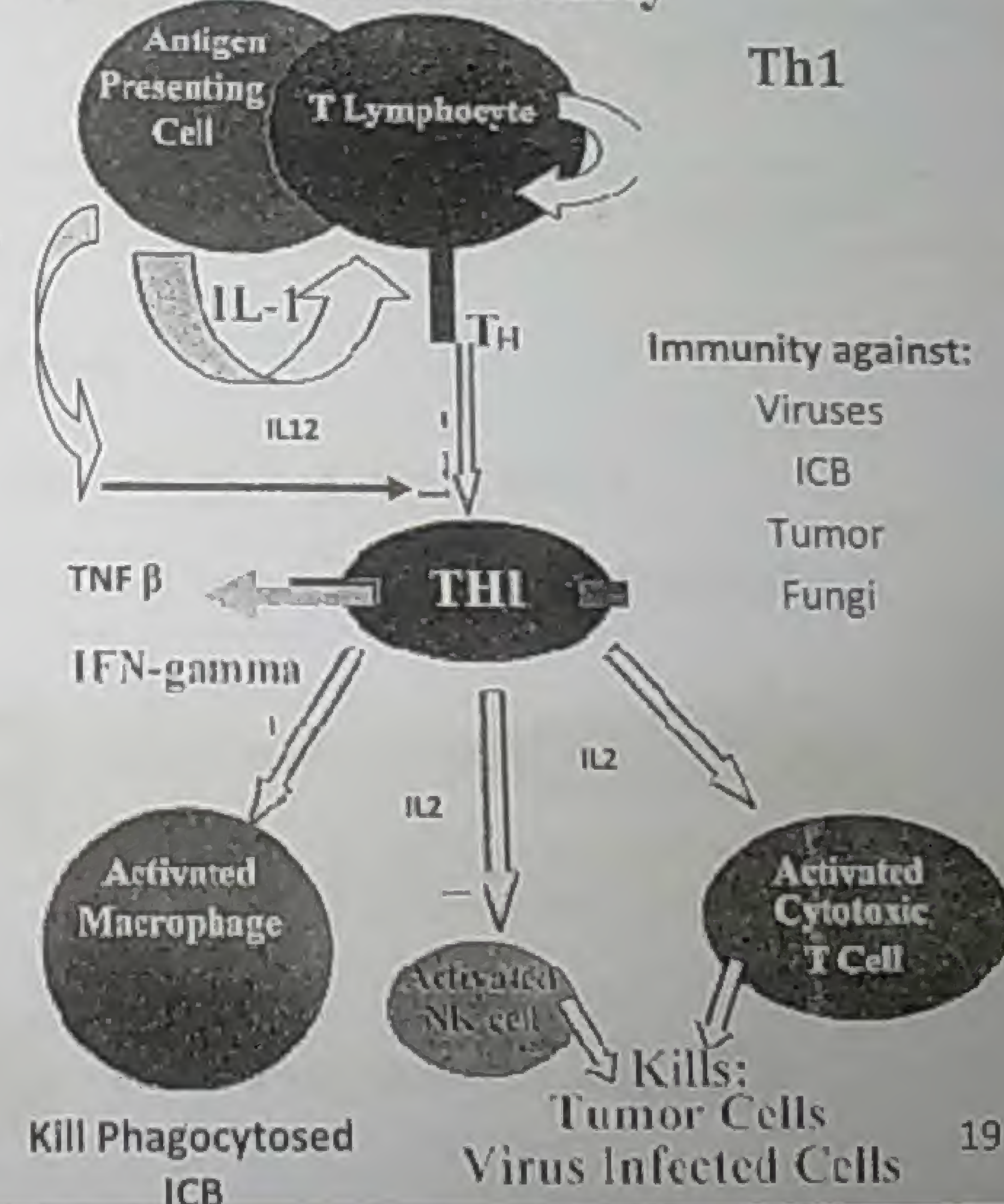
↑ cytotoxicity & ↑ INF  $\gamma$  production

2- ⊕ Differentiation of Th into Th1

↓  
↑ IFN $\gamma$  production



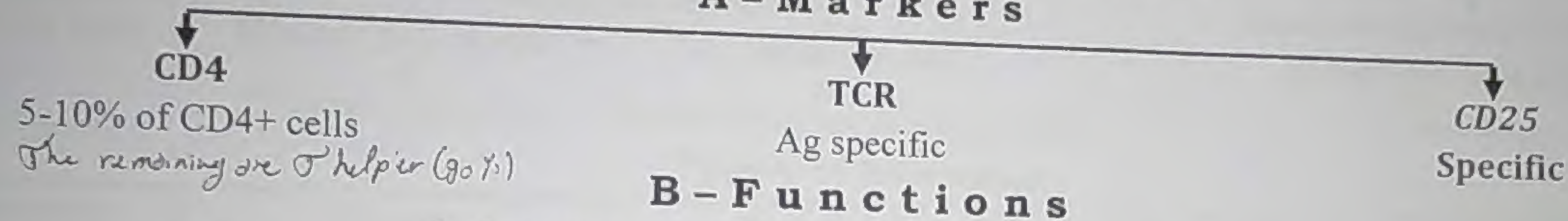
## Cell-Mediated Immunity





# Down regulation of CMIR

## I-Regulatory T cells A-Markers



### 1 - Immune suppression : by inhibitory cytokines

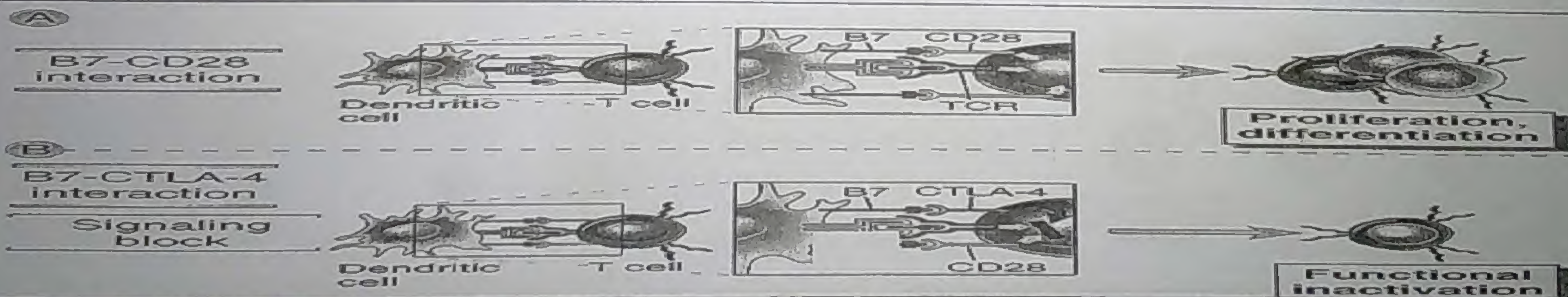
	IL10	TGFβ (transforming growth factor β)
a. On MQ	i. ↓ IL 12 production ii. ↓ MHC class II & costimulatory mol. → ↓ Ag presentation	Inhibition
b. On T cells	i. ↓ IFN γ production from Th1 <i>INF-Gamma</i> ii. ↓ expression of costimulatory mol.	⊖ proliferation & functions
c. On B cells		⊖ proliferation & Ab production

### 2 - Prevent autoimmune ds

*In 2<sup>nd</sup> lymph node* ⊖ self reactive clones that escaped -ve selection ??

## II-CTLA-4 (Cytotoxic T lymphocyte Ag) protein

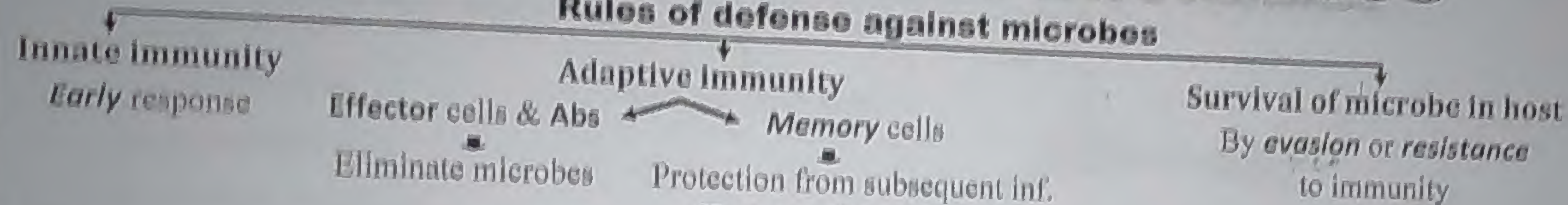
Appears on **activated** T cells (CD4+ & CD8+) → Binds B7 instead of CD28 → ⊖ T cell activation





# Immunity against microbes

## Rules of defense against microbes

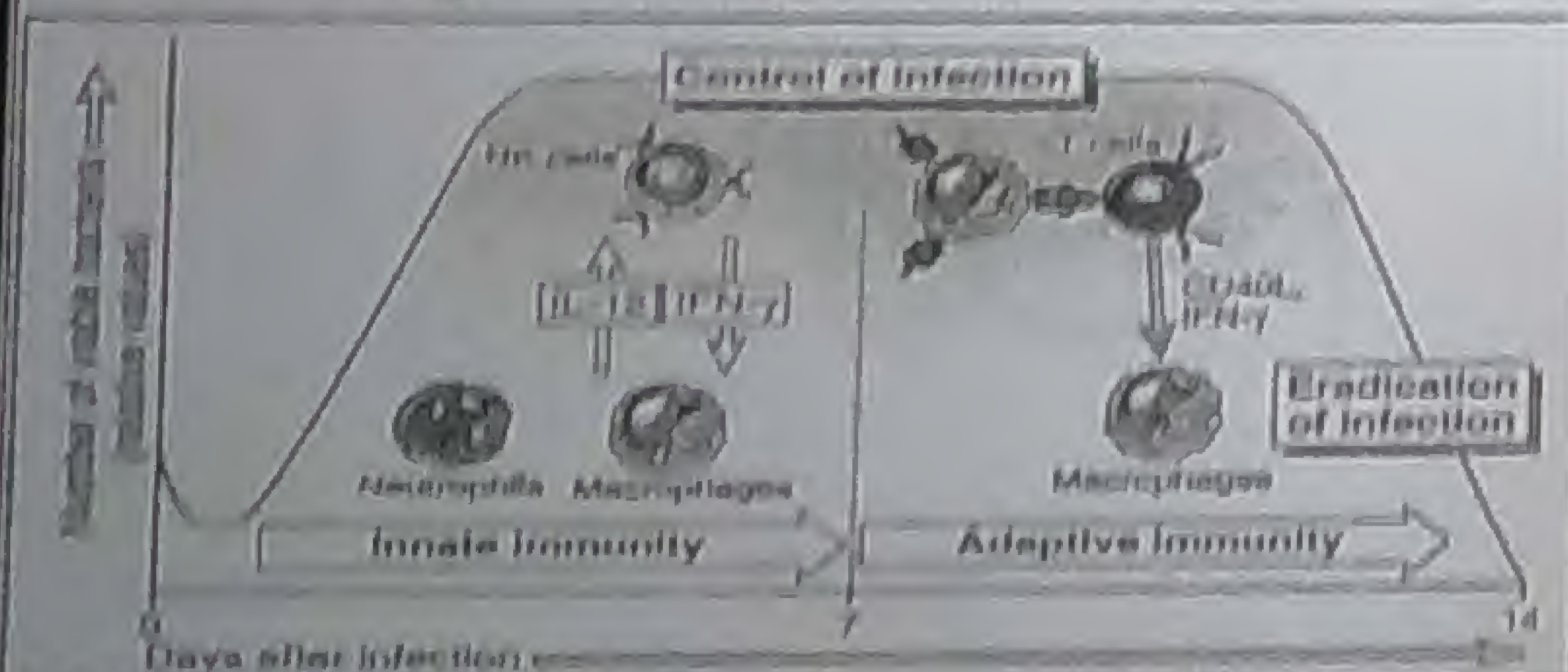
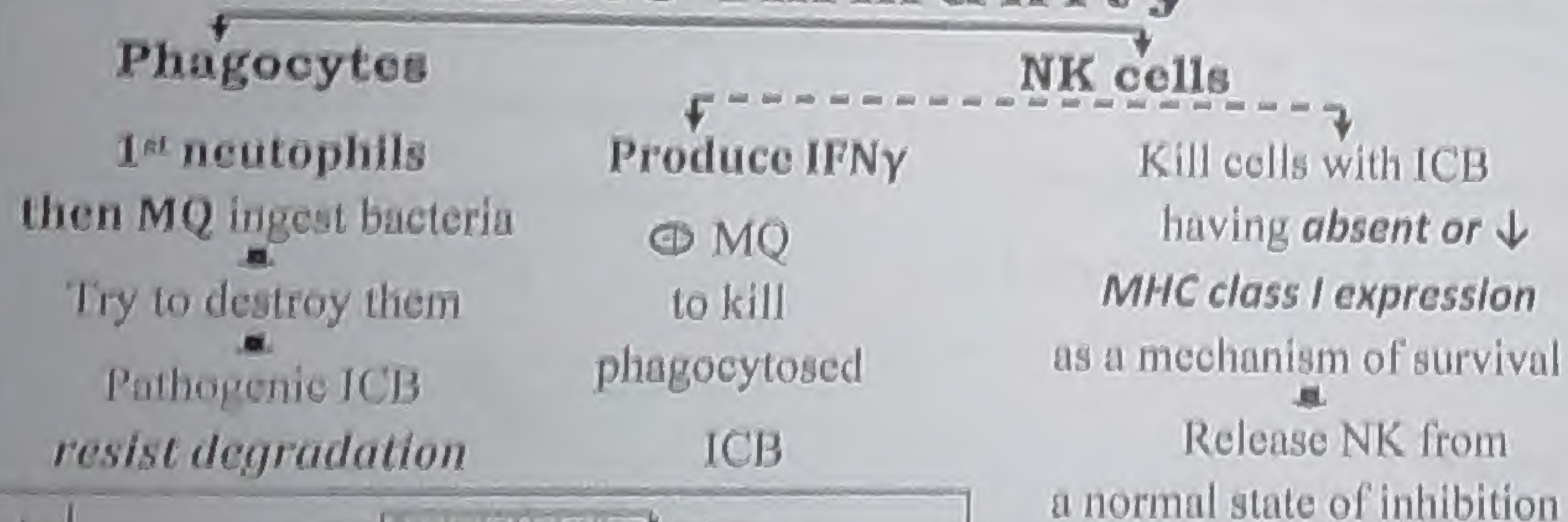


## Types of microbes

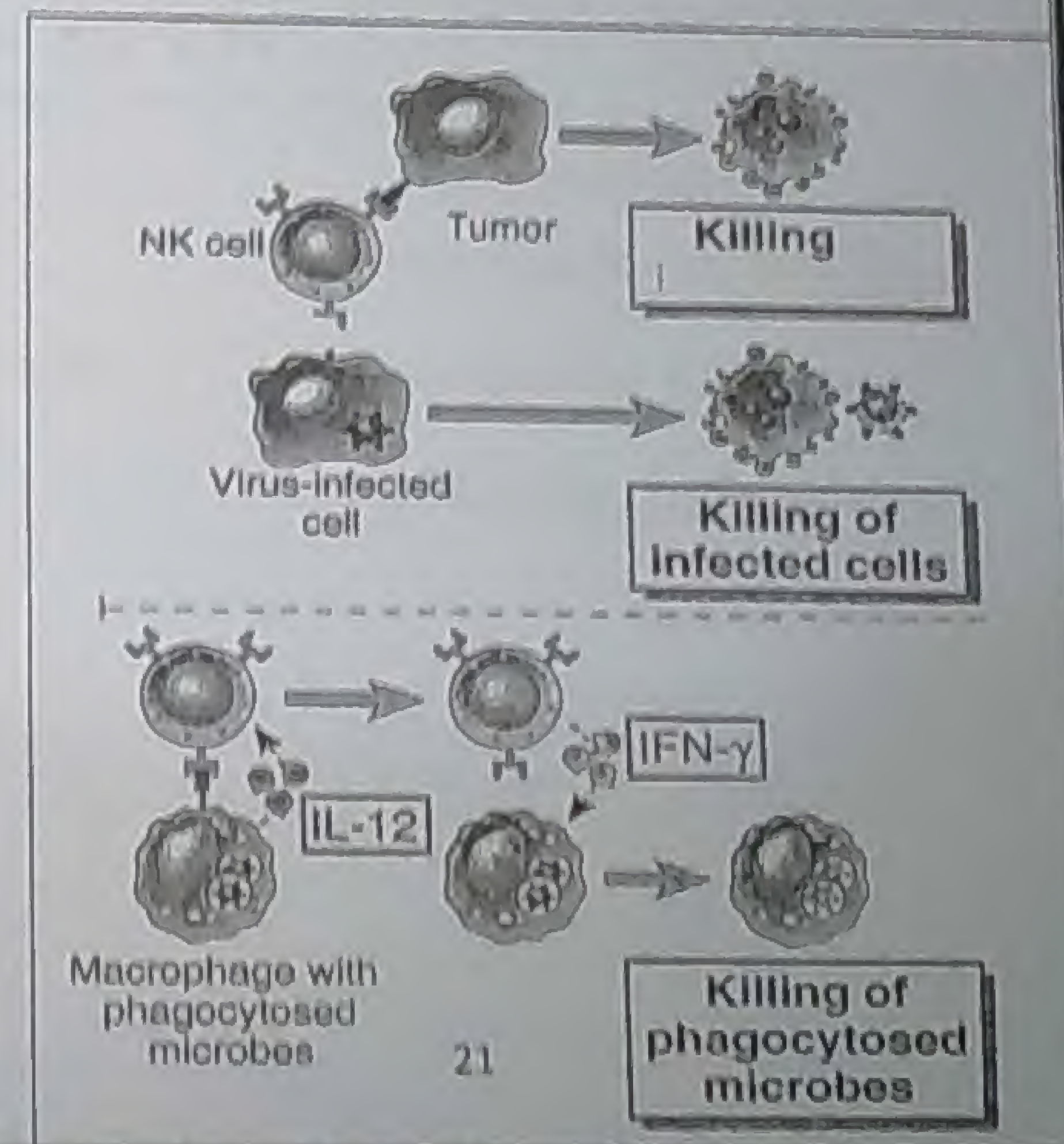
IC bacteria CMI only imm.	Viruses CMI main imm.	Fungi CMI main imm.	EC bacteria Humoral only imm.	Parasite Humoral main imm.
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## Immunity against IC bacteria

### A-Innate immunity



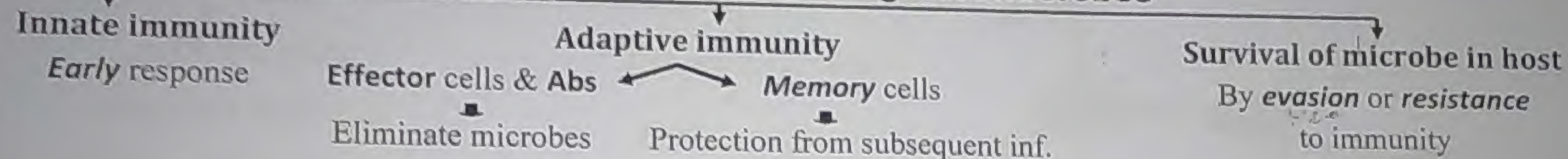
✓ Innate immunity **only** limits bacterial growth for sometimes  
Eradication requires CMI





# Immunity against microbes

## Rules of defense against microbes

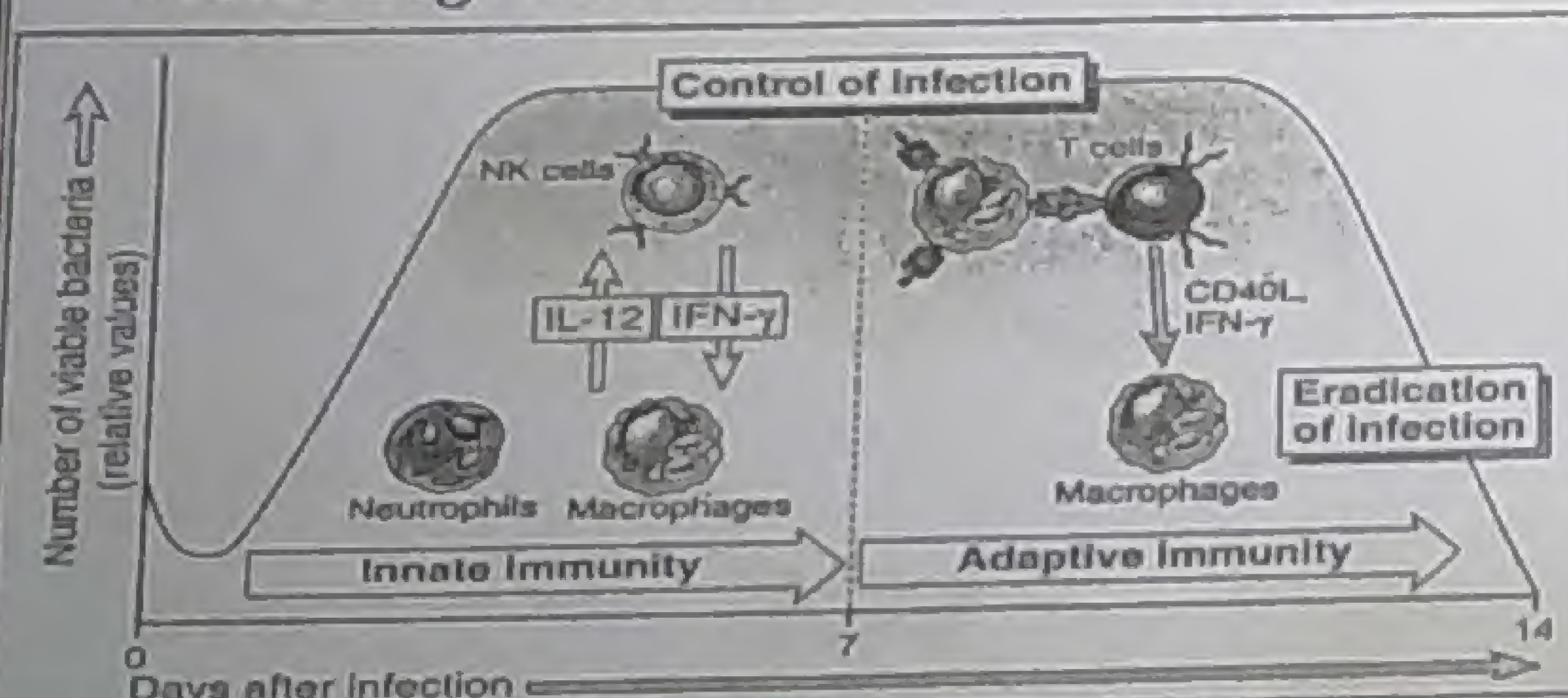
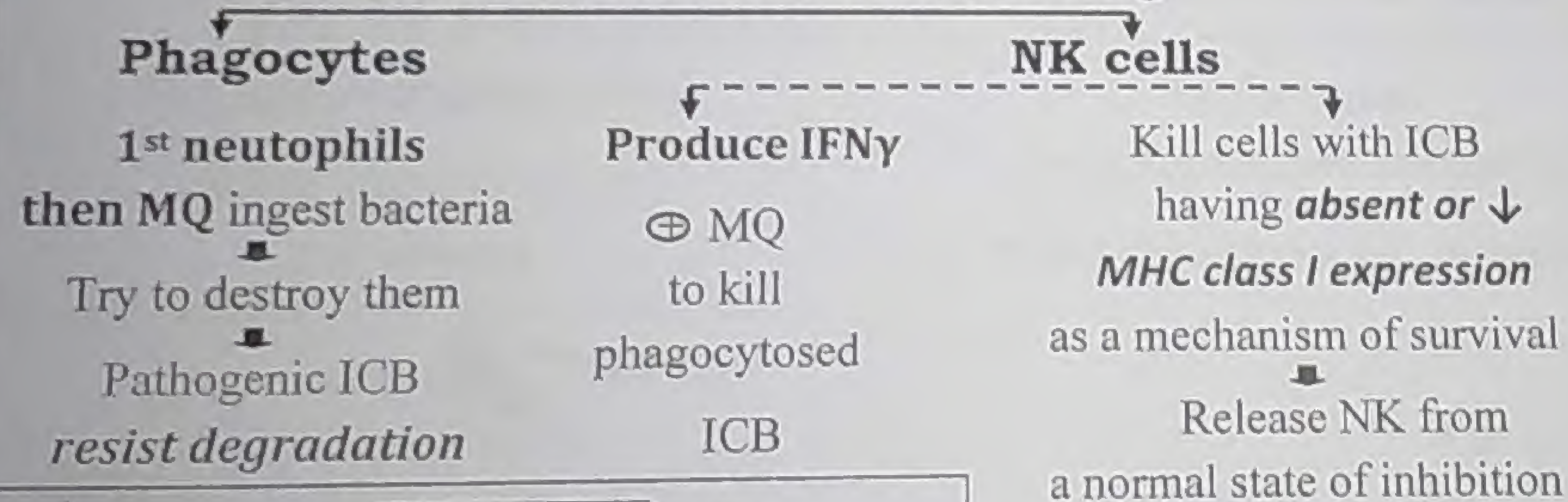


## Types of microbes

IC bacteria CMI <i>only</i> imm.	Viruses CMI <i>main</i> imm.	Fungi CMI <i>main</i> imm.	EC bacteria Humoral <i>only</i> imm.	Parasite Humoral <i>main</i> imm.
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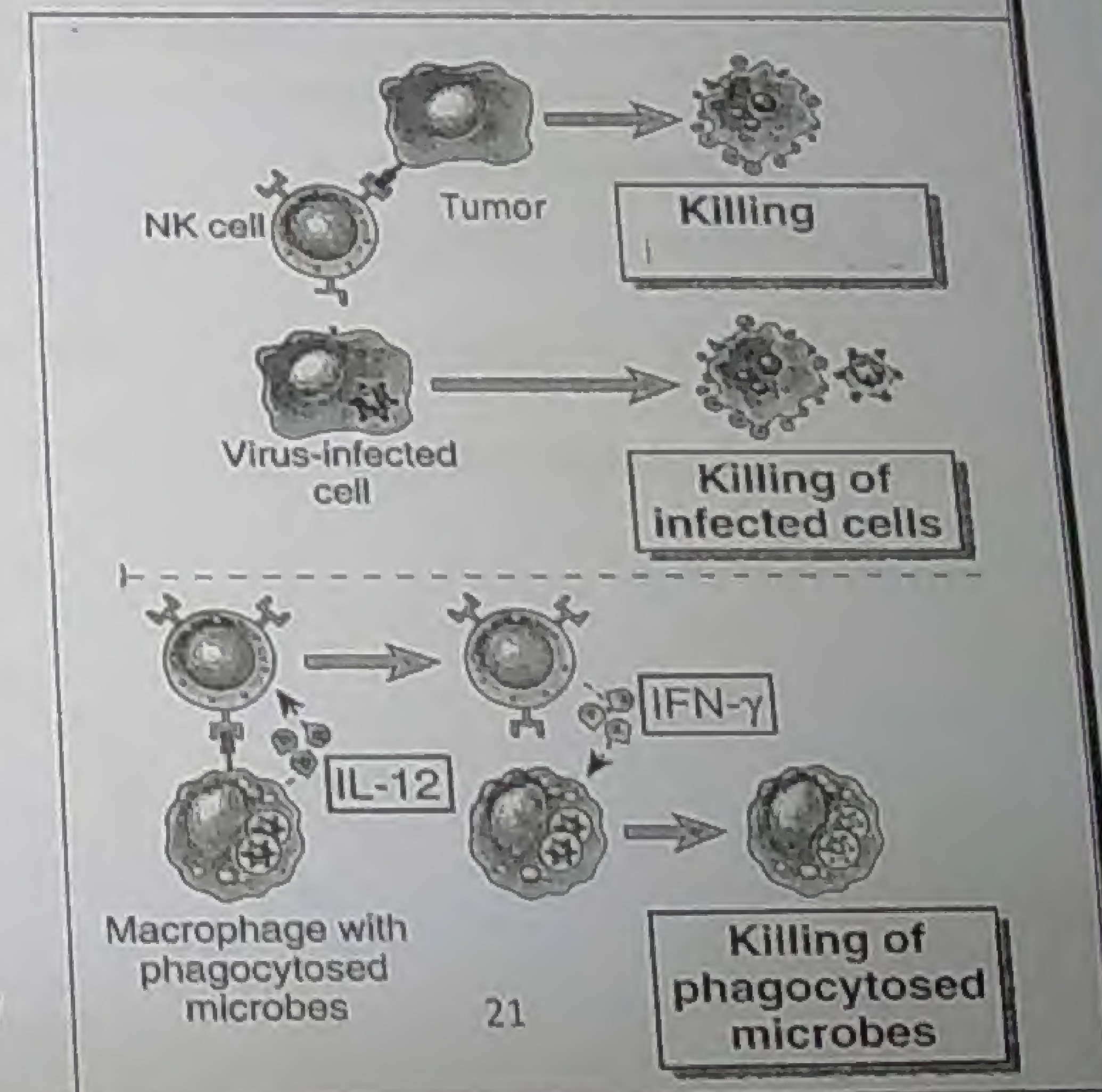
## Immunity against IC bacteria

### A - Innate immunity



✓ Innate immunity **only** limits bacterial growth for sometimes

↓  
**Eradication requires CMI**





## B - Acquired immunity

CMI is the main immunity against ICB

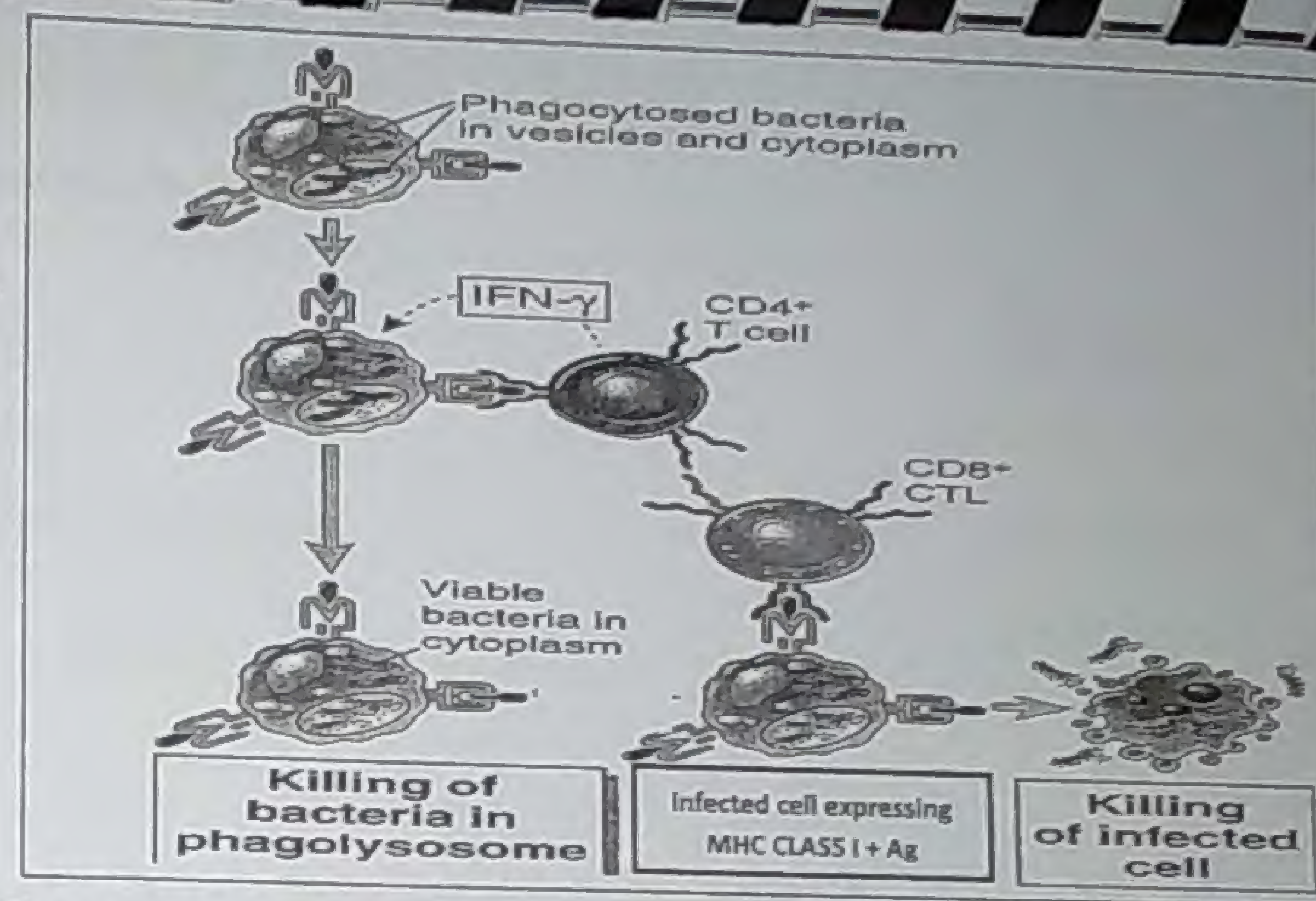
CTL kill cells  
infected with ICB  
as they express foreign Ag  
in association with *MHC class I*

Th1 secrete IFN $\gamma$

⊕ MQ to kill  
phagocytosed  
IC bacteria

♣ Pts with CMI deficiency (e.g AIDS)

are highly susceptible to infection with ICB



## C - Mechanisms of evasion of IR

Disruption of phagosome

Escape into cytoplasm  
e.g *Listeria*

Inhibition of

phagolysosomes formation

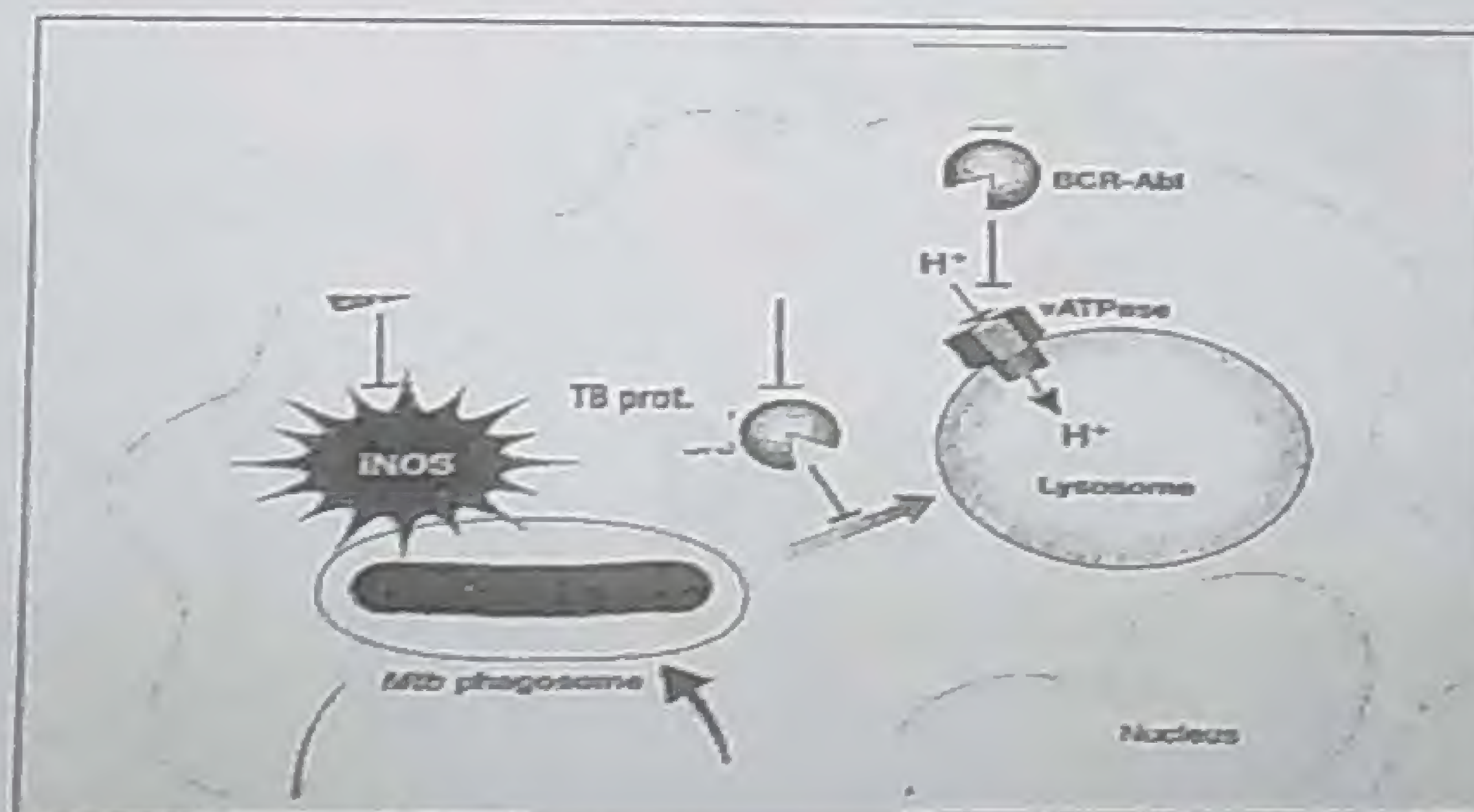
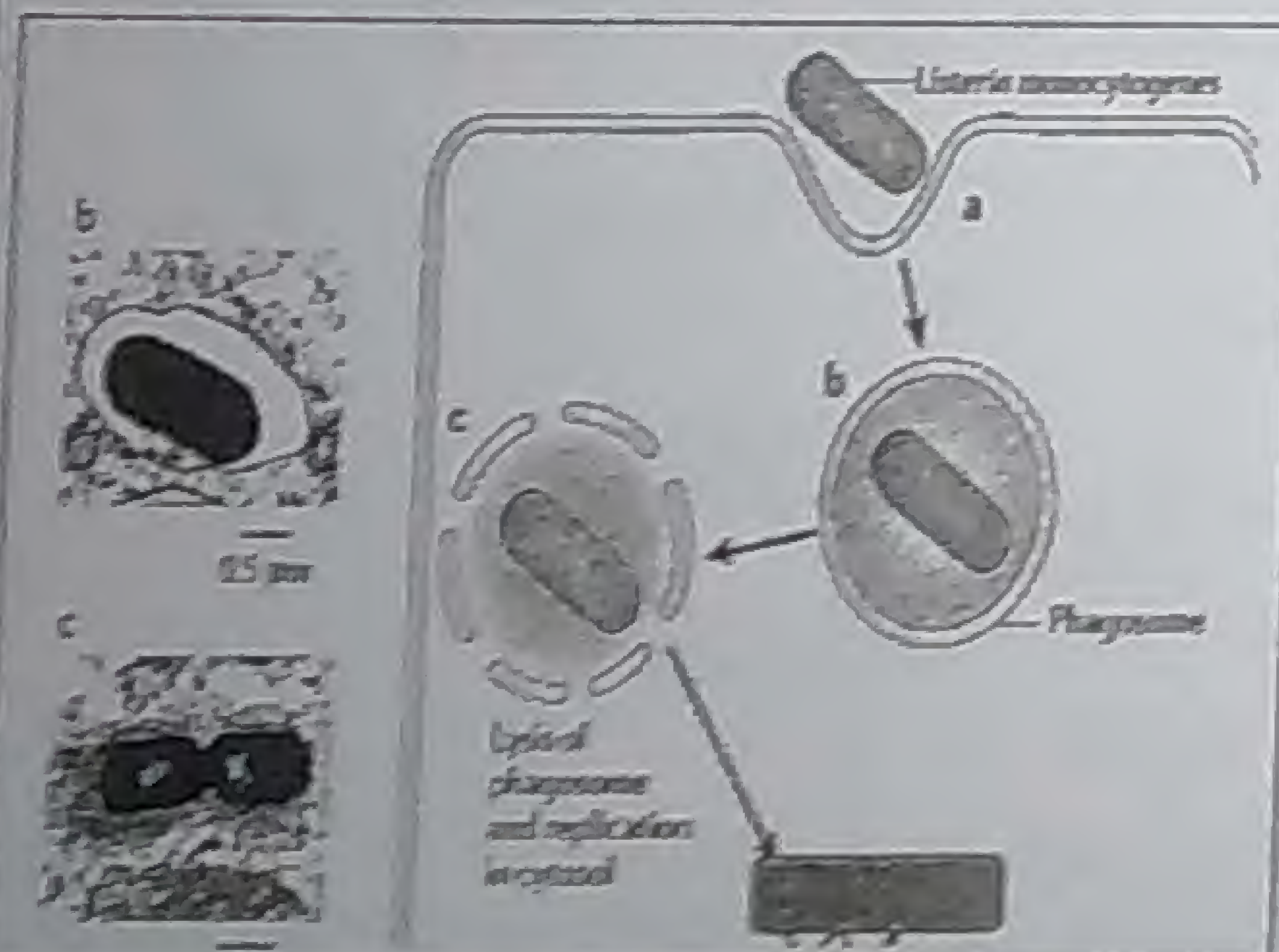
e.g ♣ *Mycobacterium TB* ♣ *Legionella*

Inactivation of

reactive O $_2$  & N $_2$  metabolites

needed for IC killing

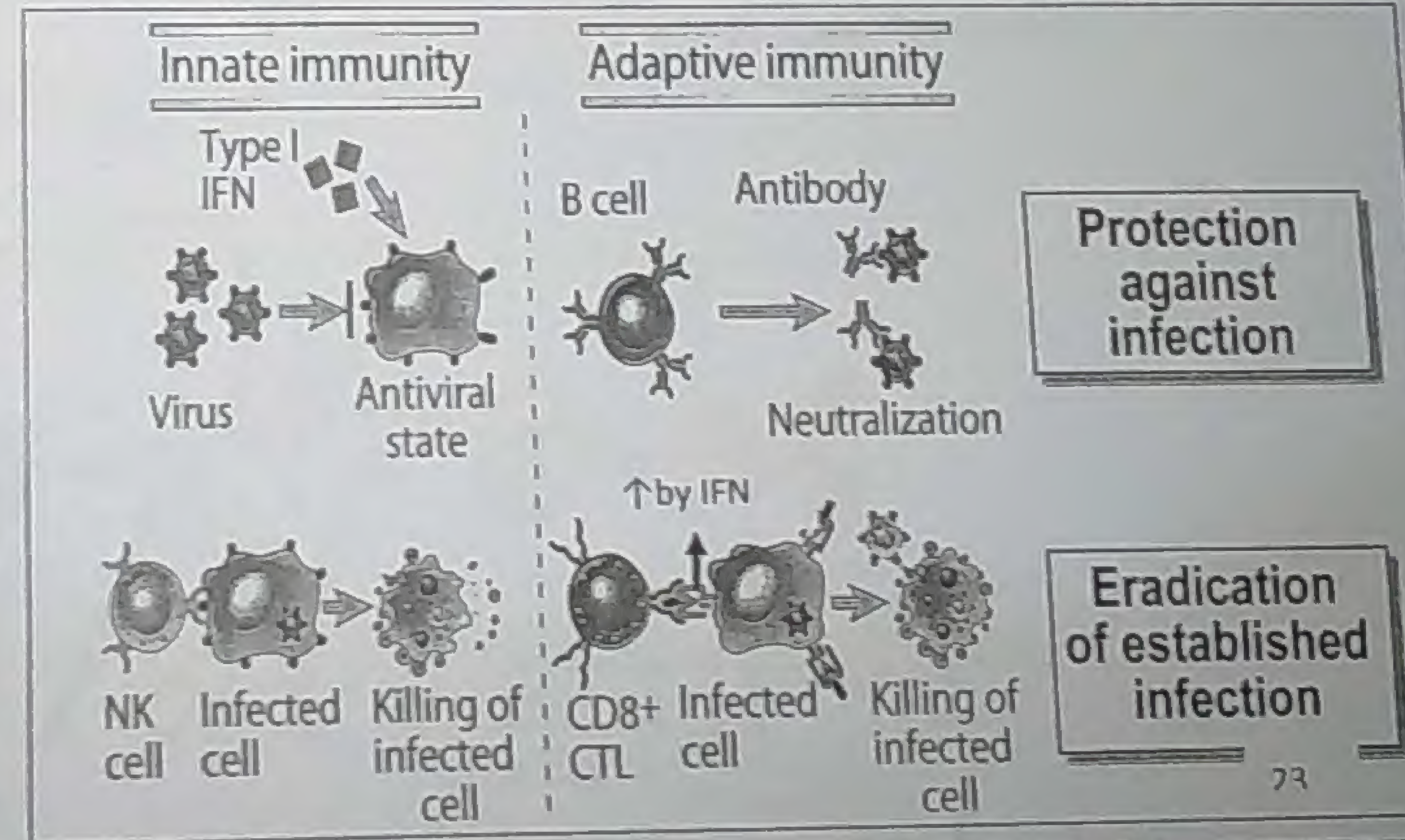
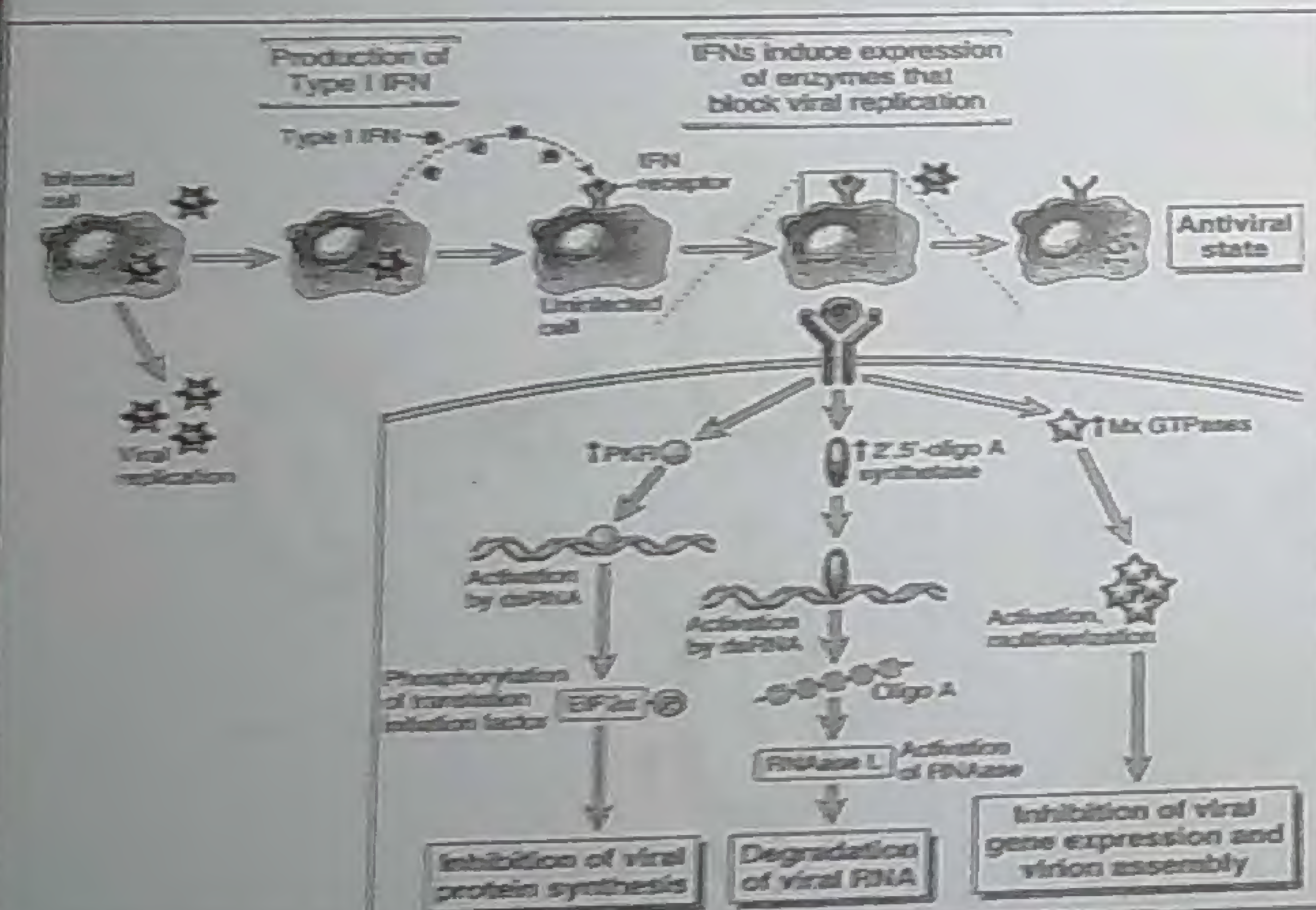
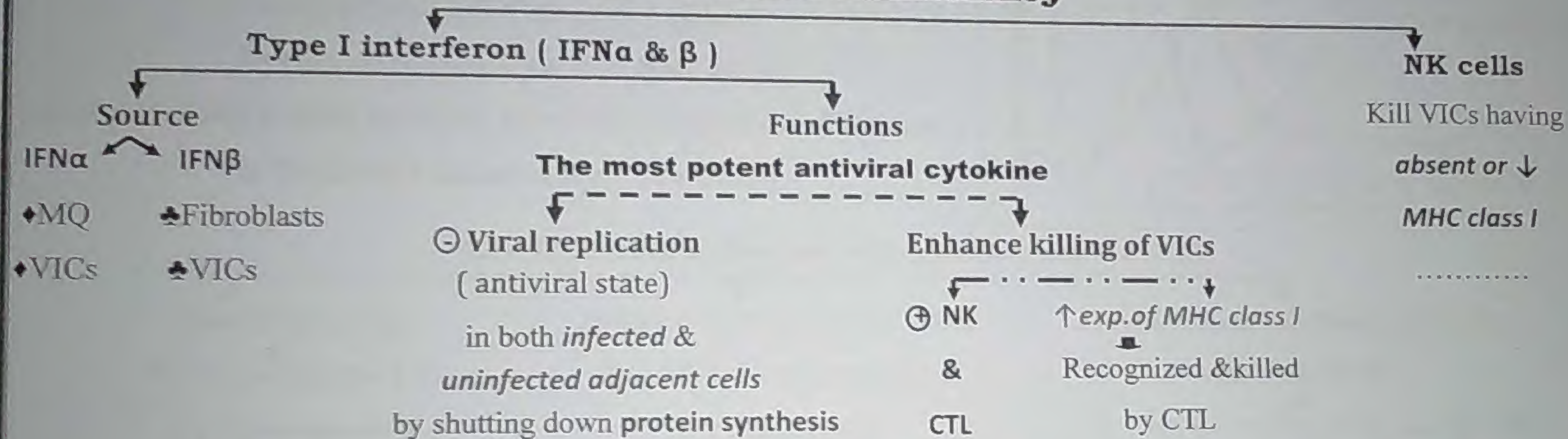
e.g *Mycobacterium leprae*





# Immunity against viruses

## A - Innate immunity





## B - Adaptive immunity

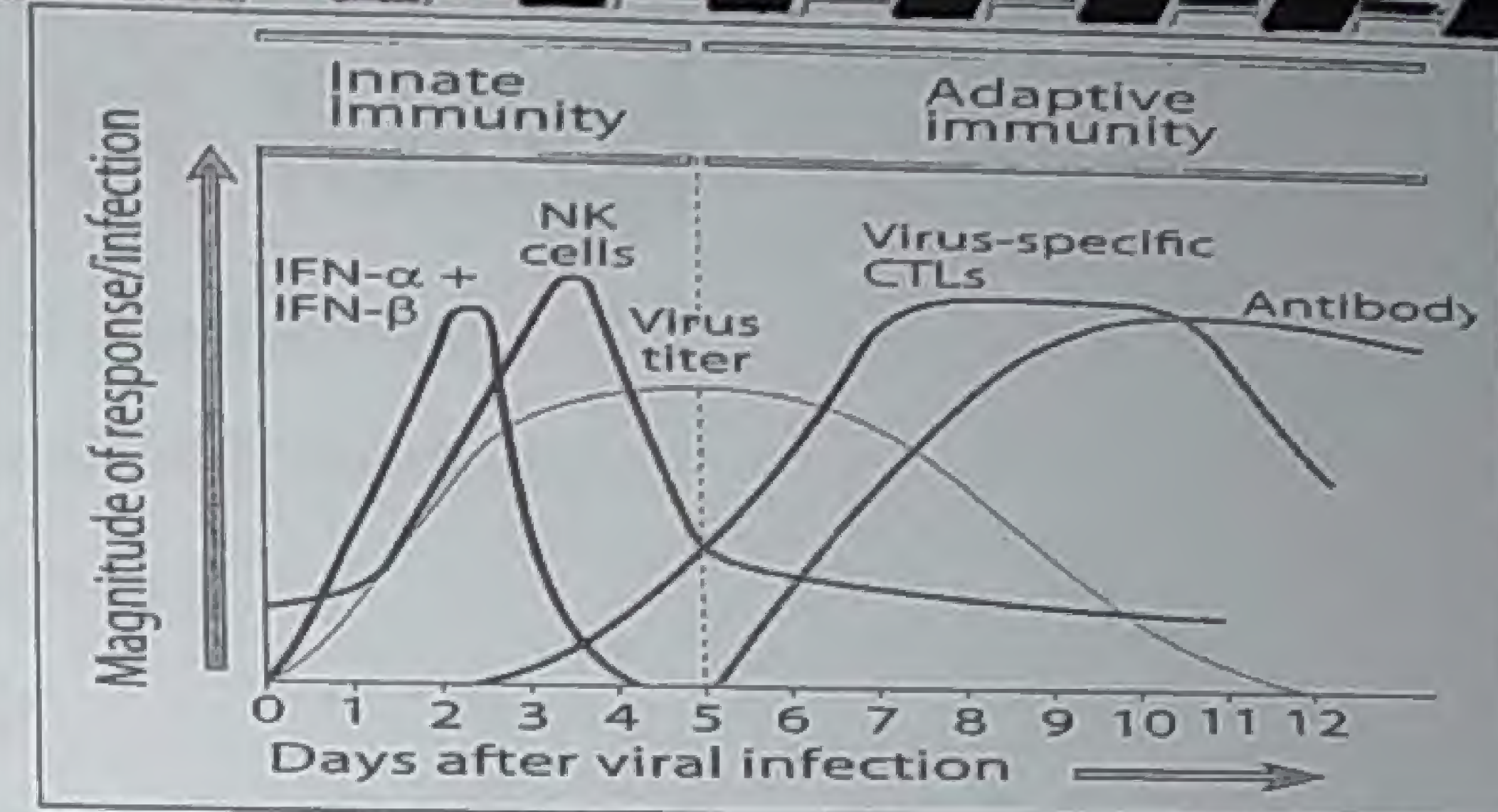
1-CMI is main immunity against viruses

CTLs (CD8+) kill VICs as they express

foreign Ag in association with *MHC class I*

⊖ Pts with CMI(e.g AIDS) are highly susceptible to infection with viruses

2-Humoral immunity : see later



## C - Mechanisms of evasion of IR

Alteration of Ags

No longer targets of IR

e.g Influenza virus

Inhibition of Ag presentation

By ↓ MHC class I expression

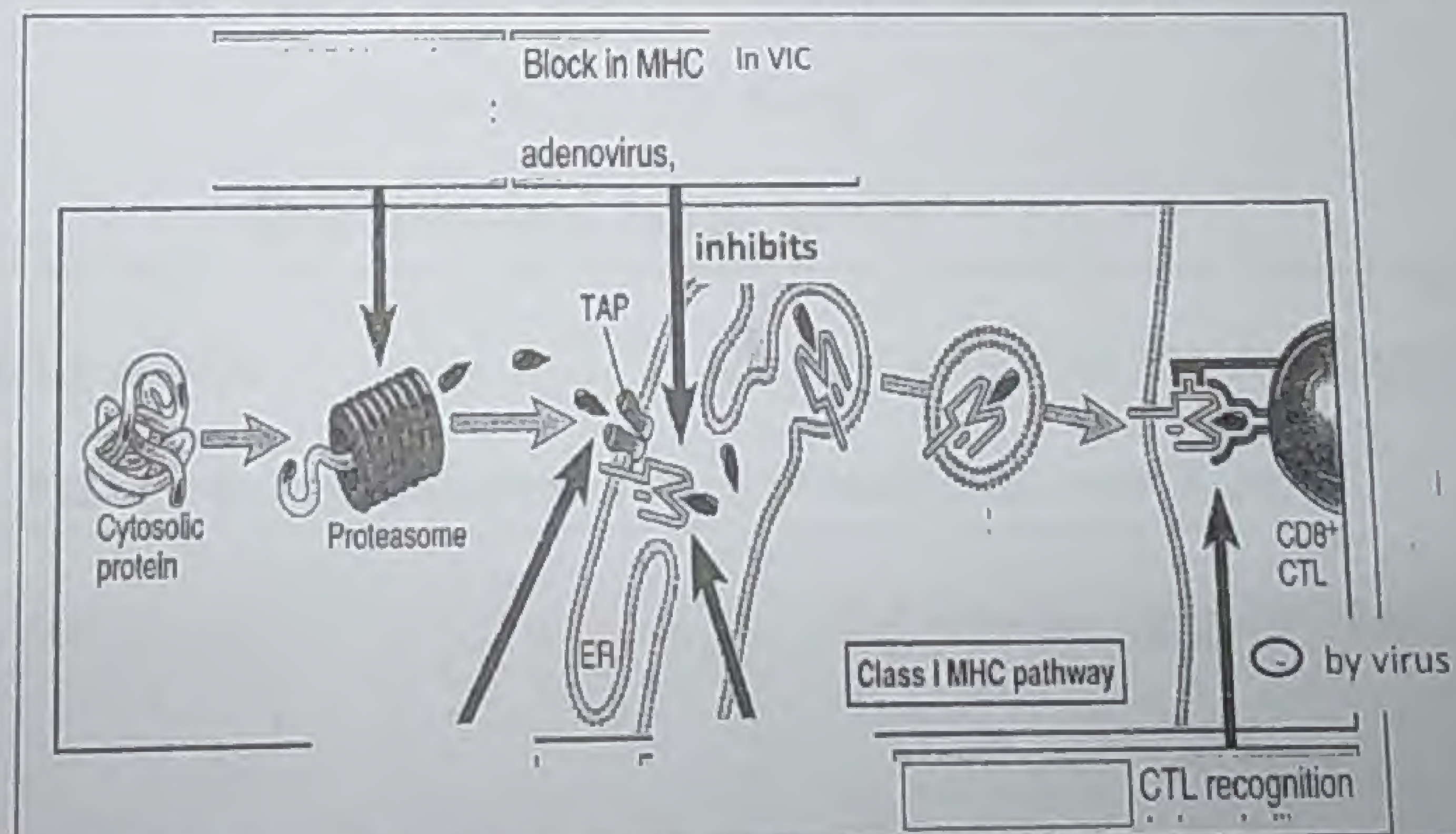
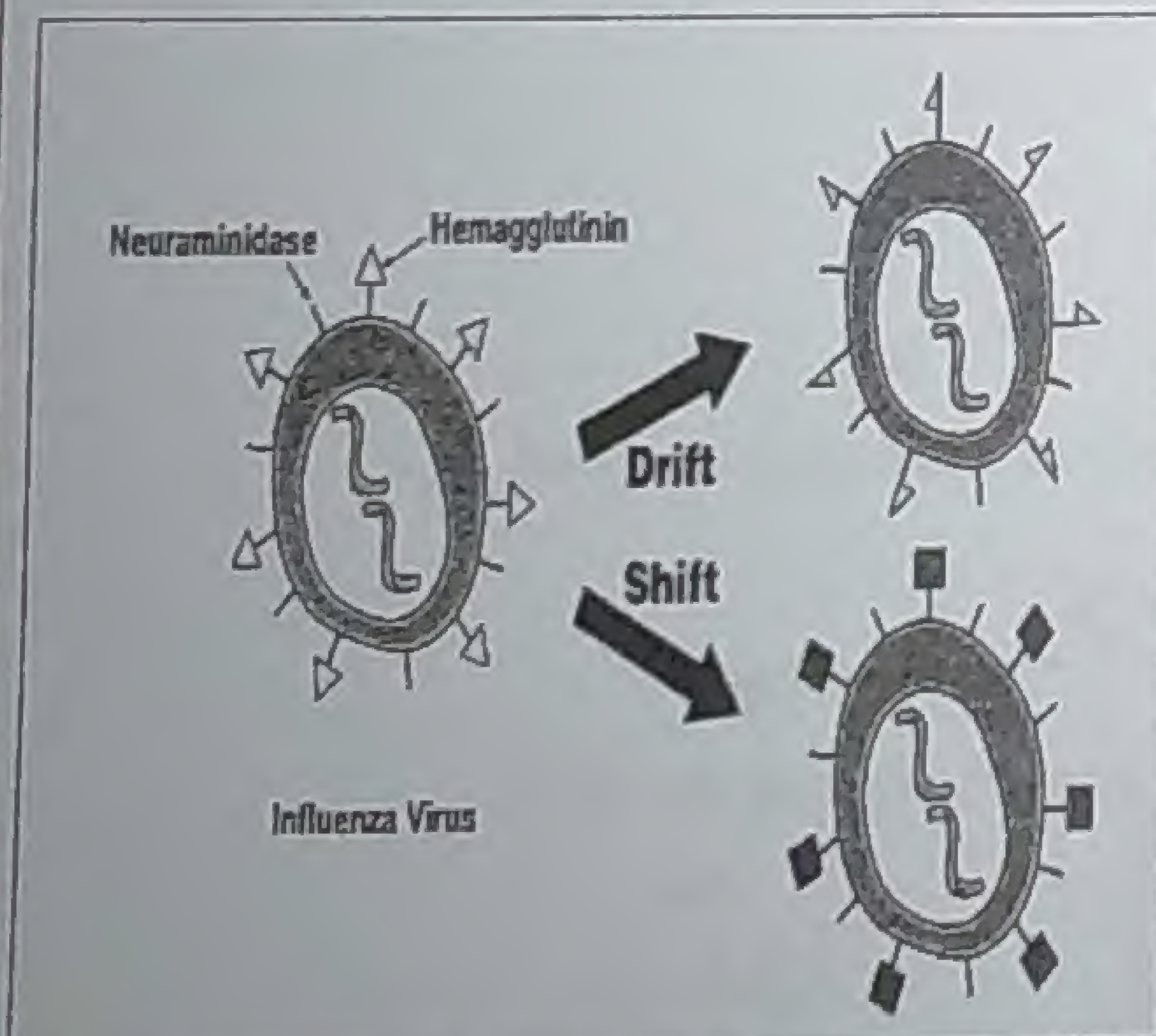
e.g Adenovirus

Production of inhibitory protein

similar to IL10

⊖ MQ&dendritic cells → ⊖ CMI

e.g Epstein-Barr virus





# Immunity against fungi

Fungi may live in EC tissue & within phagocytes

IR is a combination of responses *against EC & IC bacteria*

## A - Innate immunity

Neutrophils & MQ

Neutrophil deficiency due to BM suppression → ↑ fungal infections

## B - Adaptive immunity

### 1-CMI is the main immunity

Same mechanisms against ICB:

MQ, CD4+ & CD8+ cells cooperate

Elimination of *IC fungi*

### 2-Humoral immunity

Abs help to eradicate inf. by ADCC

Abs are useful for serological diagnosis

## C - Mechanisms of evasion of IR

↑ IL10 production

⊖ MQ

⊖ production of TNF α & IL 12

from MQ



# Pathological effects of CMI

Septic shock by superAgs

Type IV hypersensitivity

Autoimmune ds



## SuperAgs

### A-Special Characters & Effects

They aren't processed by APCs

Bind to MHC class II outside Ag binding groove

Bind only to *V region* of a particular  $\beta$  chain of TCR

⊕ large n= of Th cells with different Ag specificities

(Non specific or polyclonal activation)

↑↑ release of IFN $\gamma$  & IL2

↑↑ release of IL1, 12 & TNF $\alpha$  from MQ

T cells become *refractory* to ⊕

Septic shock

Anergy

### B-Examples

Bacterial toxins

Viral proteins

Staph. aureus

Strept. pyogenes

• Epstein Barr V

• Enterotoxins

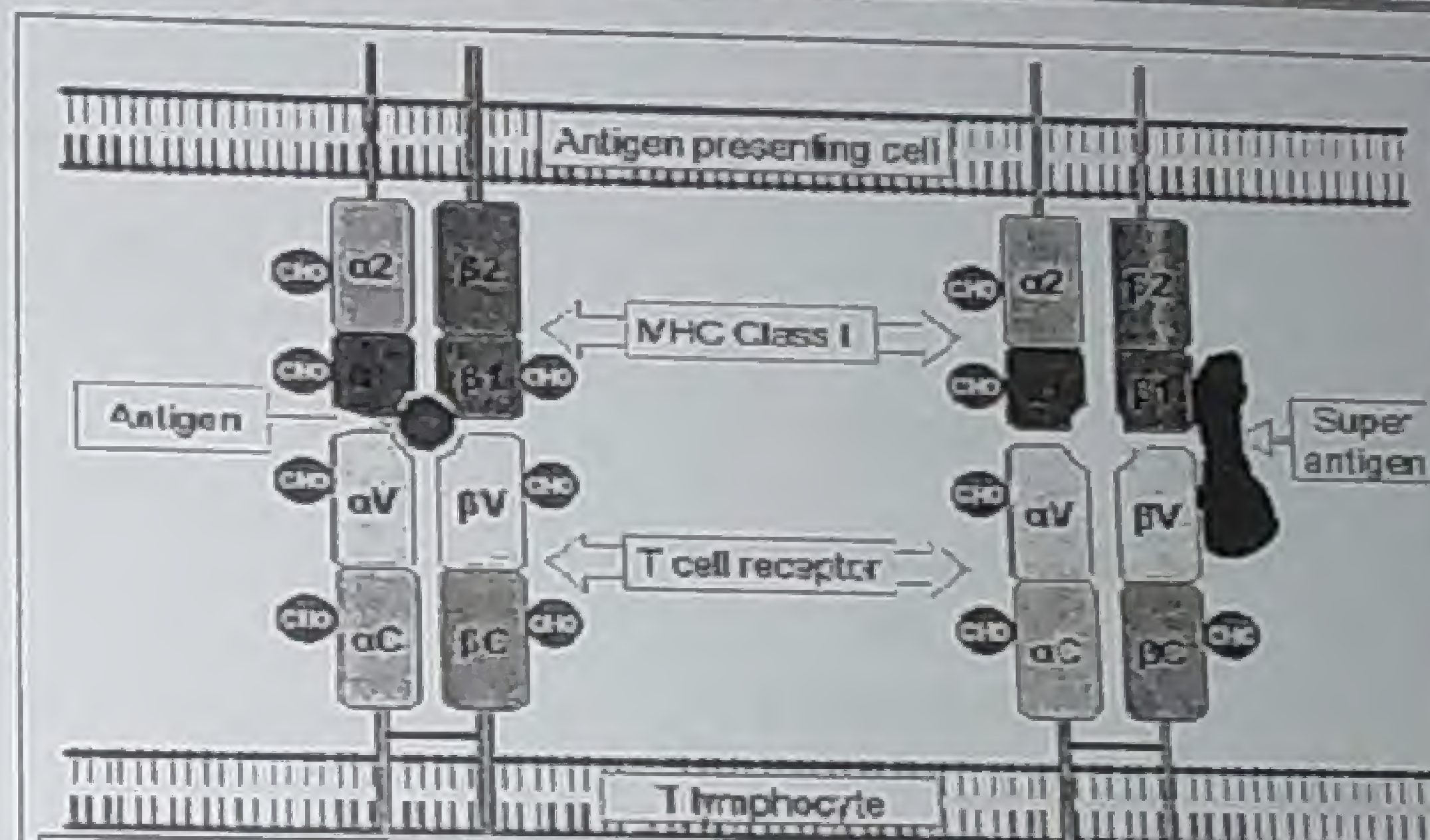
Pyrogenic

• Rabies V

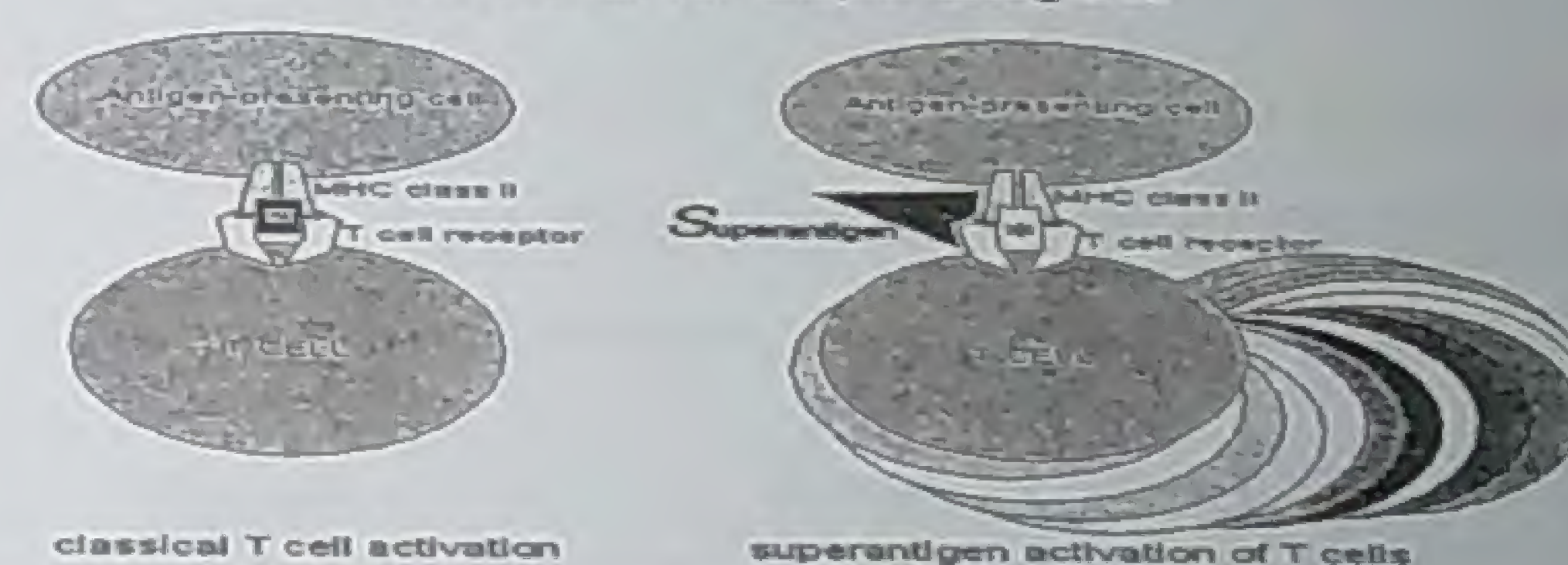
• Toxic shock

toxins

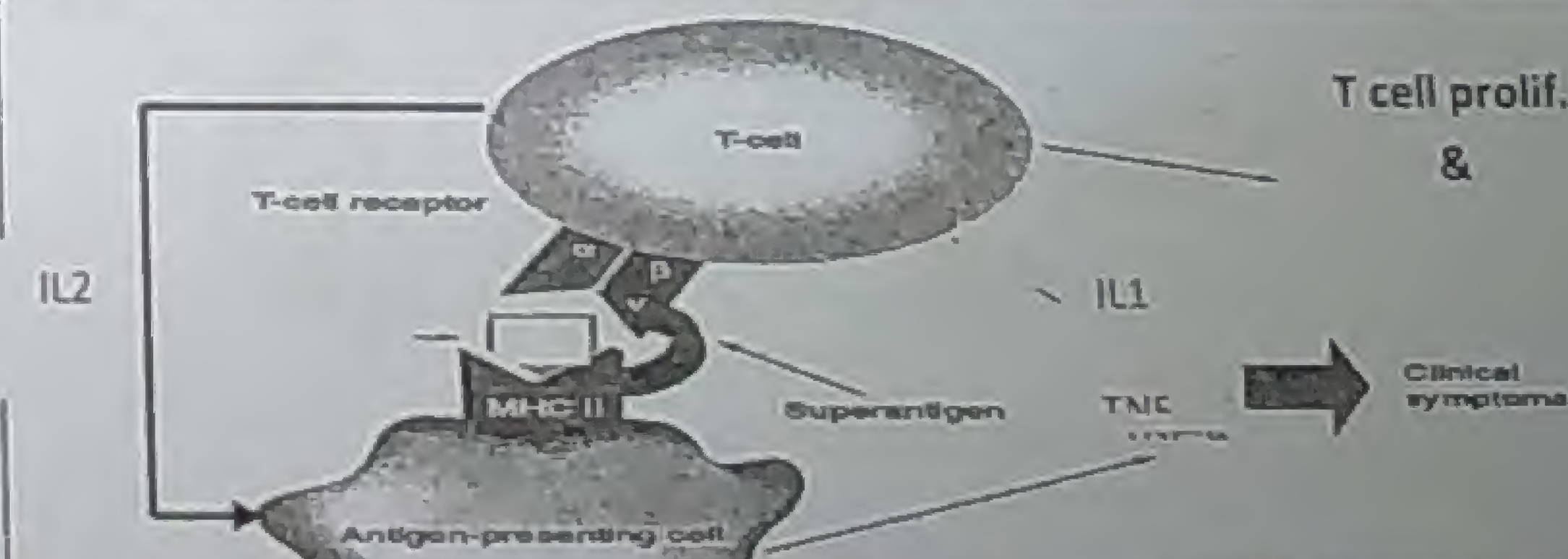
syndrome toxin



Classical vs. Superantigens



Medscape





# Septic Shock

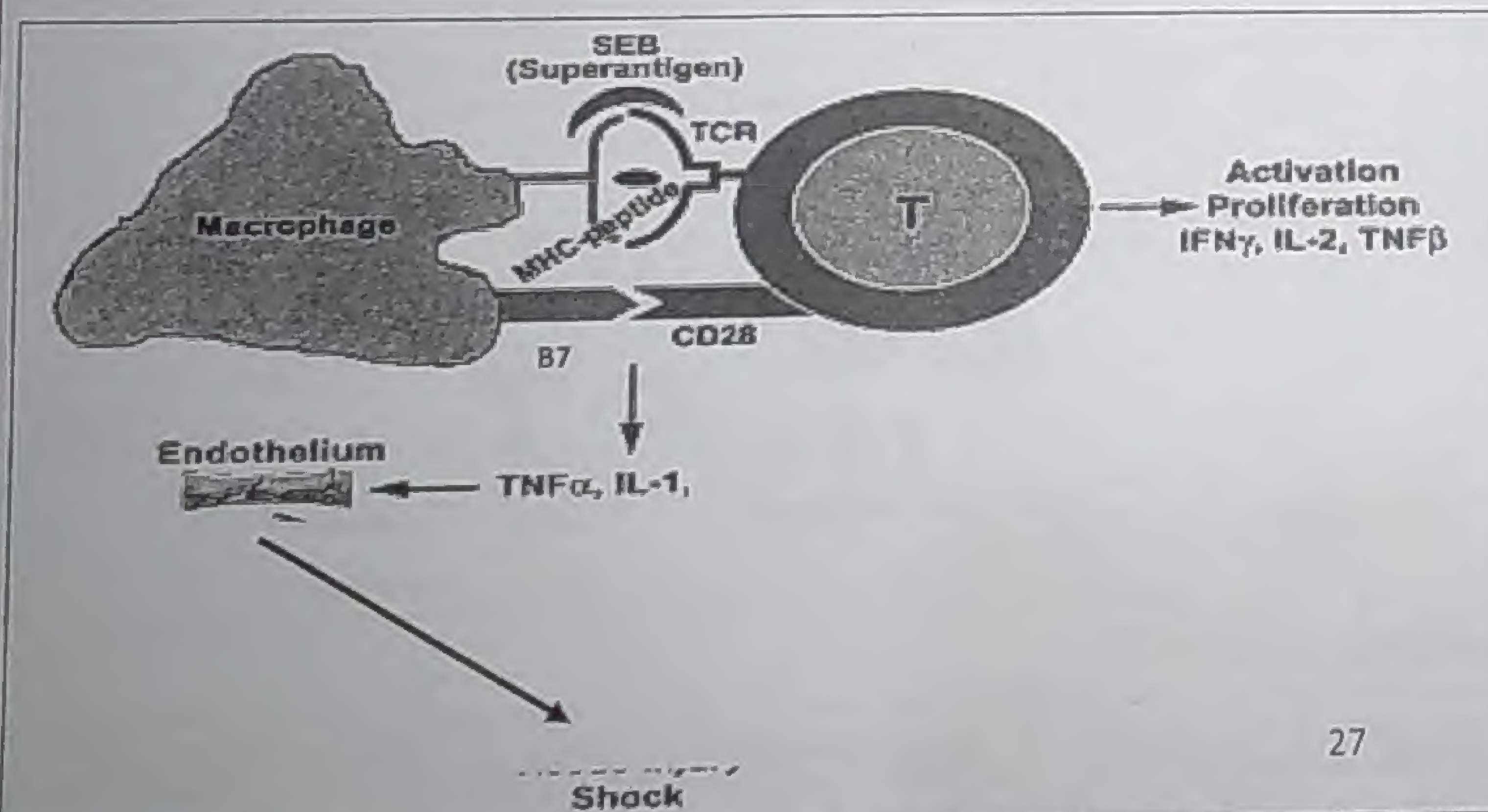
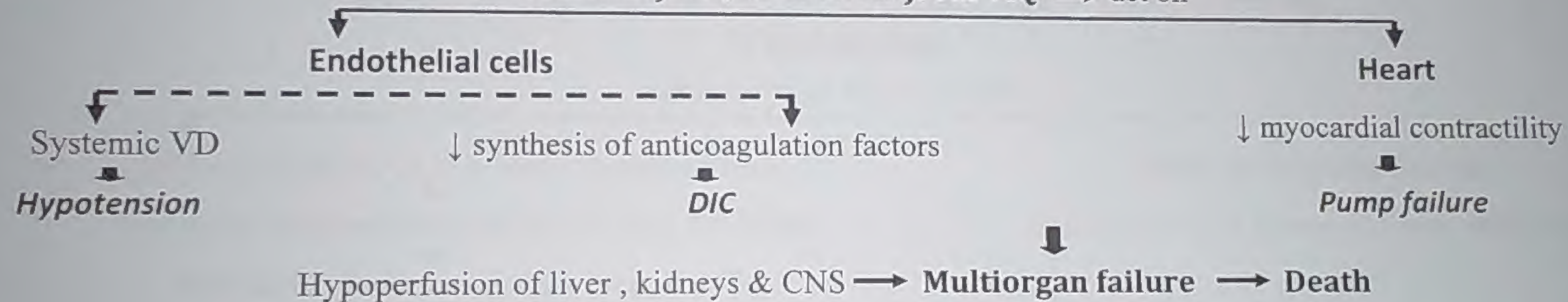
## Definition

Cytokine-induced pathological consequences of superAgs

## Mechanism

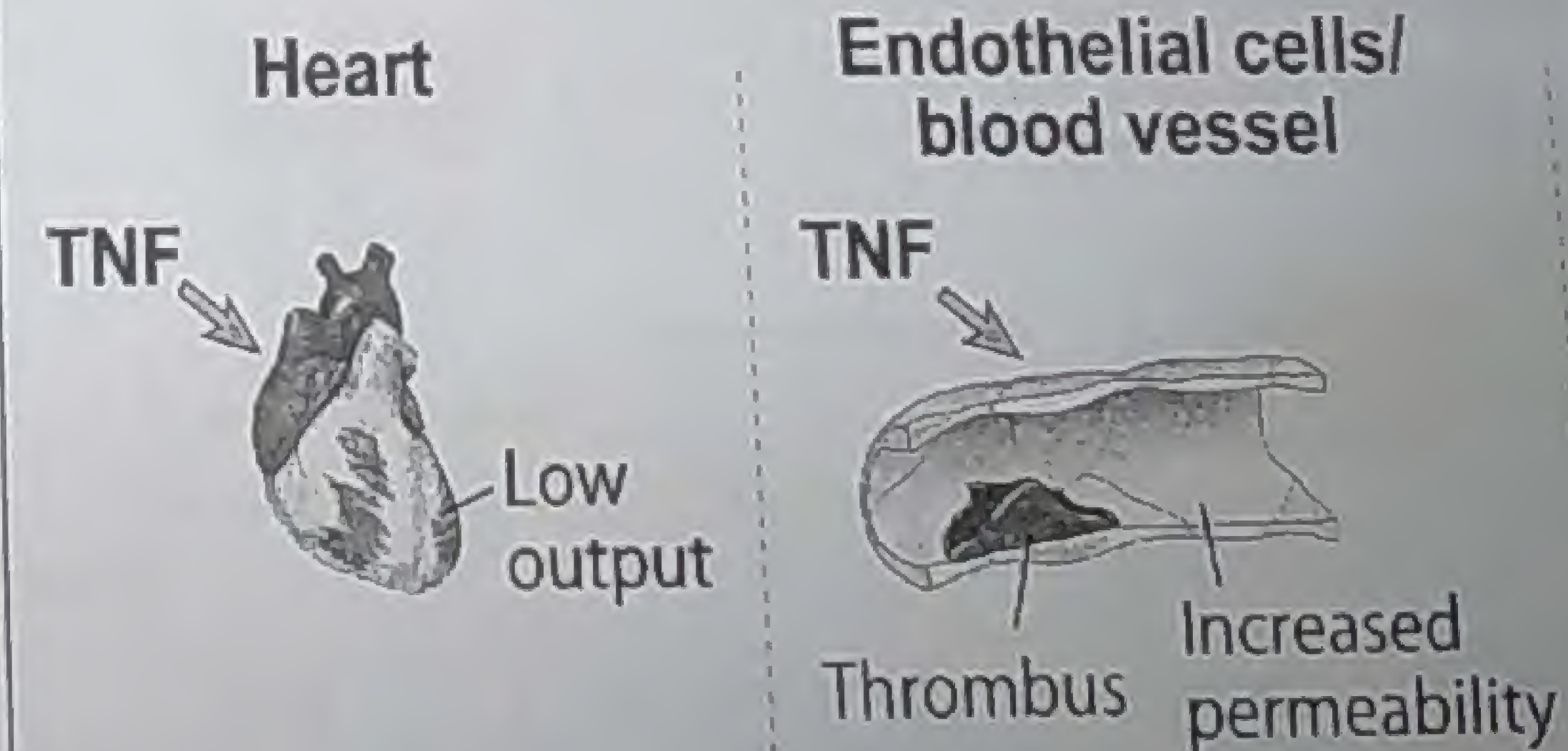
↑↑ release of  $\text{IFN}\gamma$  &  $\text{IL}2$  from  $\oplus$  large n= of Th cells with different Ag specificities

↑↑ release of  $\text{IL}1$ ,  $12$  &  $\text{TNF}\alpha$  from MQ → act on



27

## Systemic pathological effects



S  
n



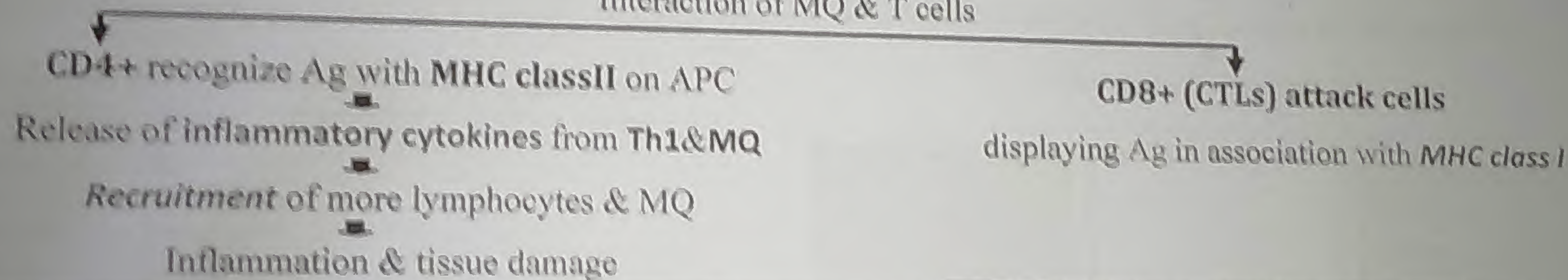
# Hypersensitivity

Definition Exaggerated IR resulting in tissue damage	Time 2 <sup>nd</sup> contact with Ag	Classification (according to mechanism of injury) Ab mediated Type I, II & III	T cell mediated Type IV
--	--	--	----------------------------

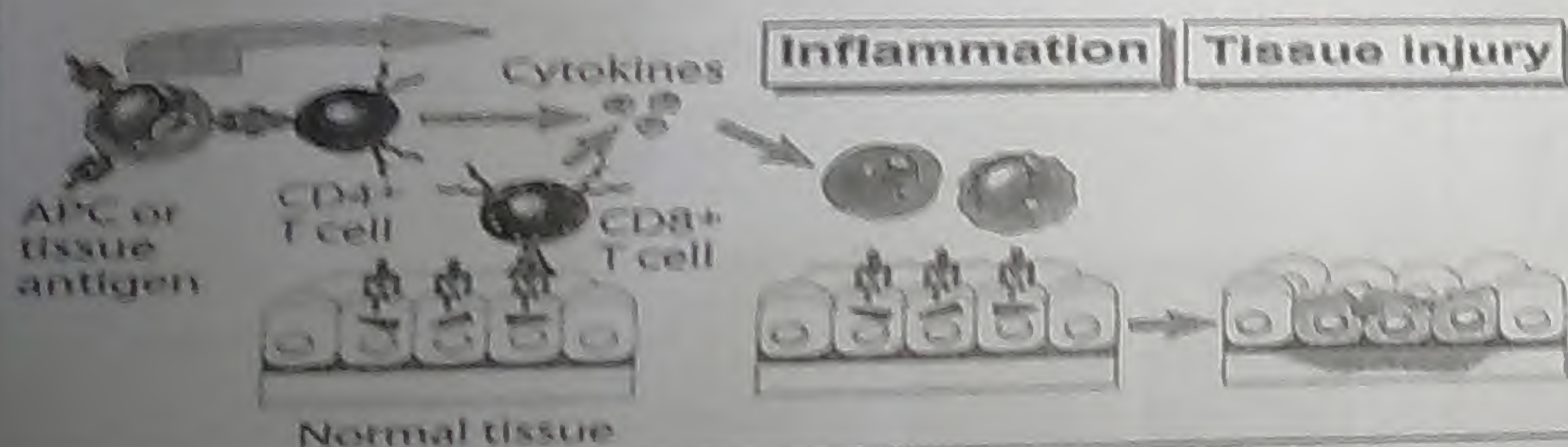
## Type IV (Delayed or CM) Hypersensitivity

### Mechanism

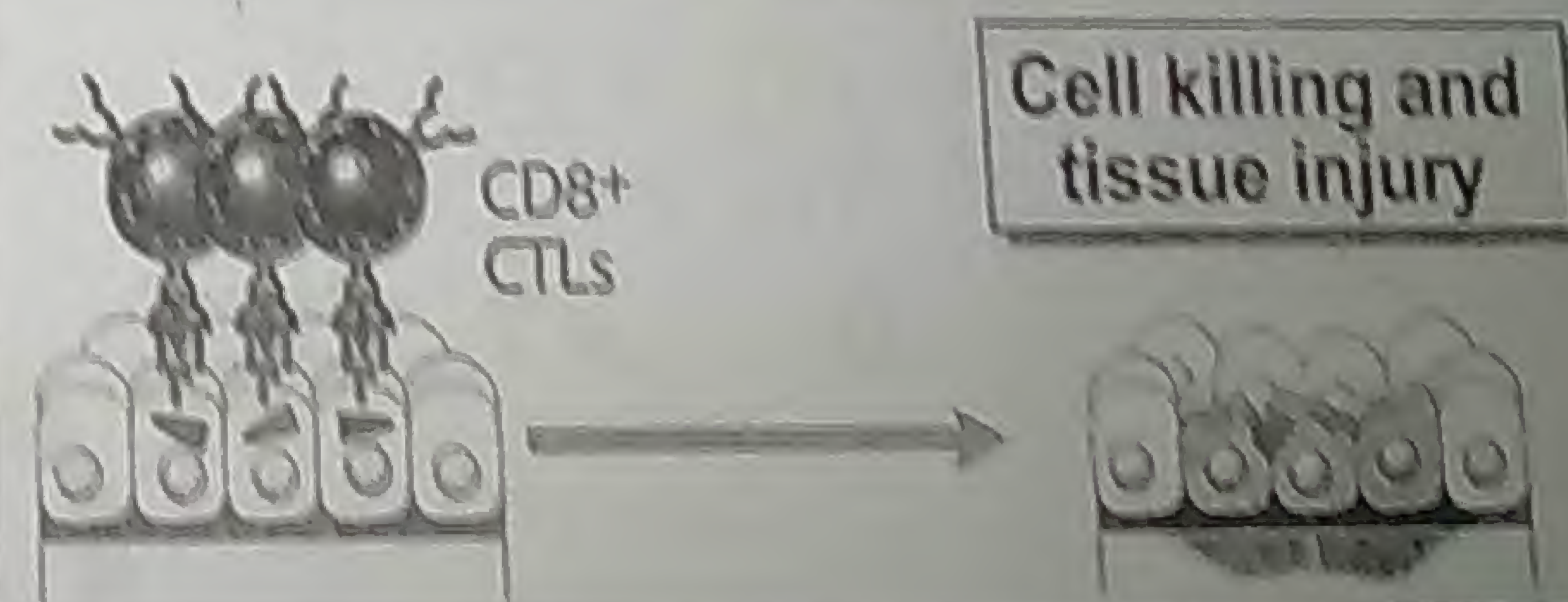
Interaction of MQ & T cells



#### Cytokine-mediated inflammation



#### T cell-mediated cytotoxicity



### Clinical applications

Tuberculin test	Granulomatous ds	Contact dermatitis	DM	Acute & chronic graft rejection
-----------------	------------------	--------------------	----	---------------------------------



# Tuberculin test

## Method & +ve result

ID injection of PPD (purified protein derivative)  
of *Mycobacterium TB*

↓ 48 hrs

*Erythema & Induration*

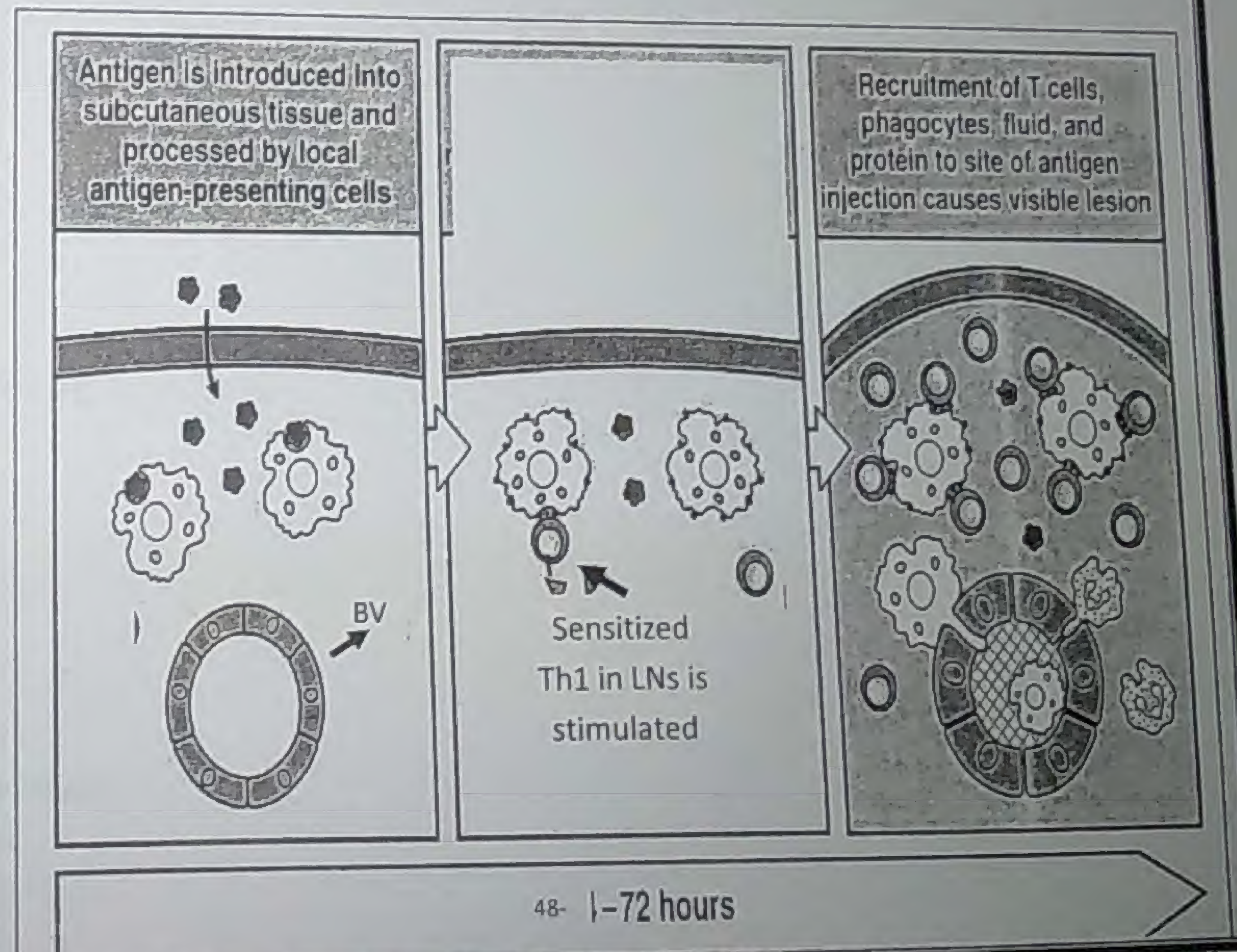
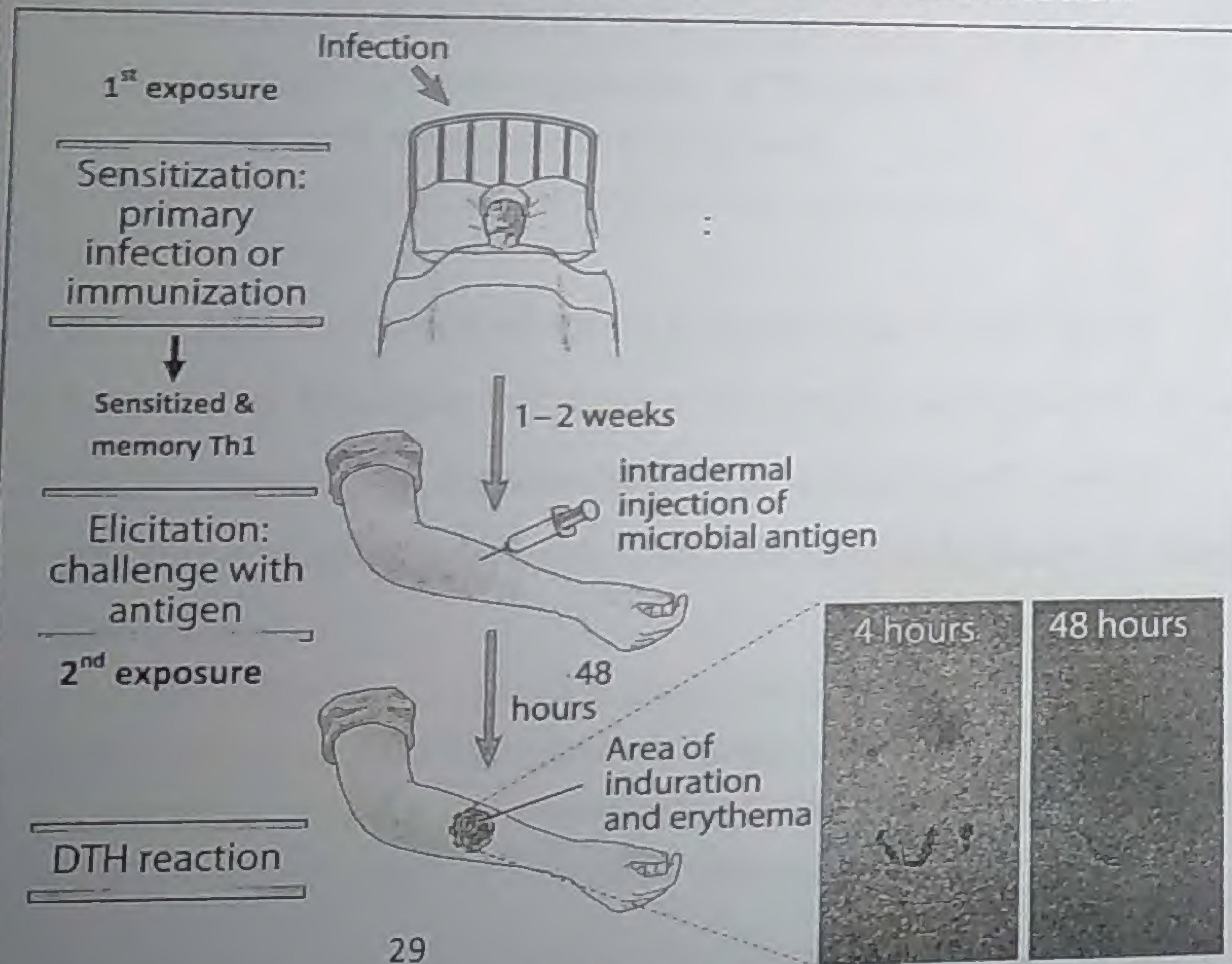
in a person previously exposed to TB bacilli due to:

- Subclinical ds
- Clinical ds
- BCG vaccination

## Mechanism

MQ & dendritic cells at site of injection uptake PPD  
↓  
DCs migrate to LNs → present Ag to sensitized Th1  
↓  
*Sensitized Th1 migrate to site of Ag & secrete cytokines*

↓  
Recruitment of more lymphocytes & MQ with VD  
↓  
Induration & Erythema





## Essay Questions

1-Compare & Contrast between:

- i. T cell receptor & B cell receptor
- ii. T cell dependent & T cell independent Ags.
- iii. 1ry & 2ry IR
- iv. Opsonization & ADCC
- v. The 3 pathways of complement activation
- vi. IR to IC & EC pathogens.

2-Give an account on

- i. Isotype switch
- ii. Secretory component
- iii. IL4
- iv. Mechanisms of evasion of IR by EC bacteria & parasites
- v. +ve feedback & cross regulation of Th subsets
- vi. Cytokines that stimulate hematopoiesis
- vii. Regulatory proteins of complement components.
- viii. Hapten

3-Give a short account on Clinical aspects of complement.

4-Enumerate biological activities of complement, give an account on 1 of them

5-Define heterophil Ag, mention its practical applications

6- Name mechanisms by which Abs eliminate Ag from the body

7-Give reason :

- i. T helper cell is important in isotype switch of B cell
- ii. C3b is an important complement component
- iii. Inherited deficiency of complement may lead to angioneurotic edema
- iv. Both interferon & IL 4 influence outcome of class switch.



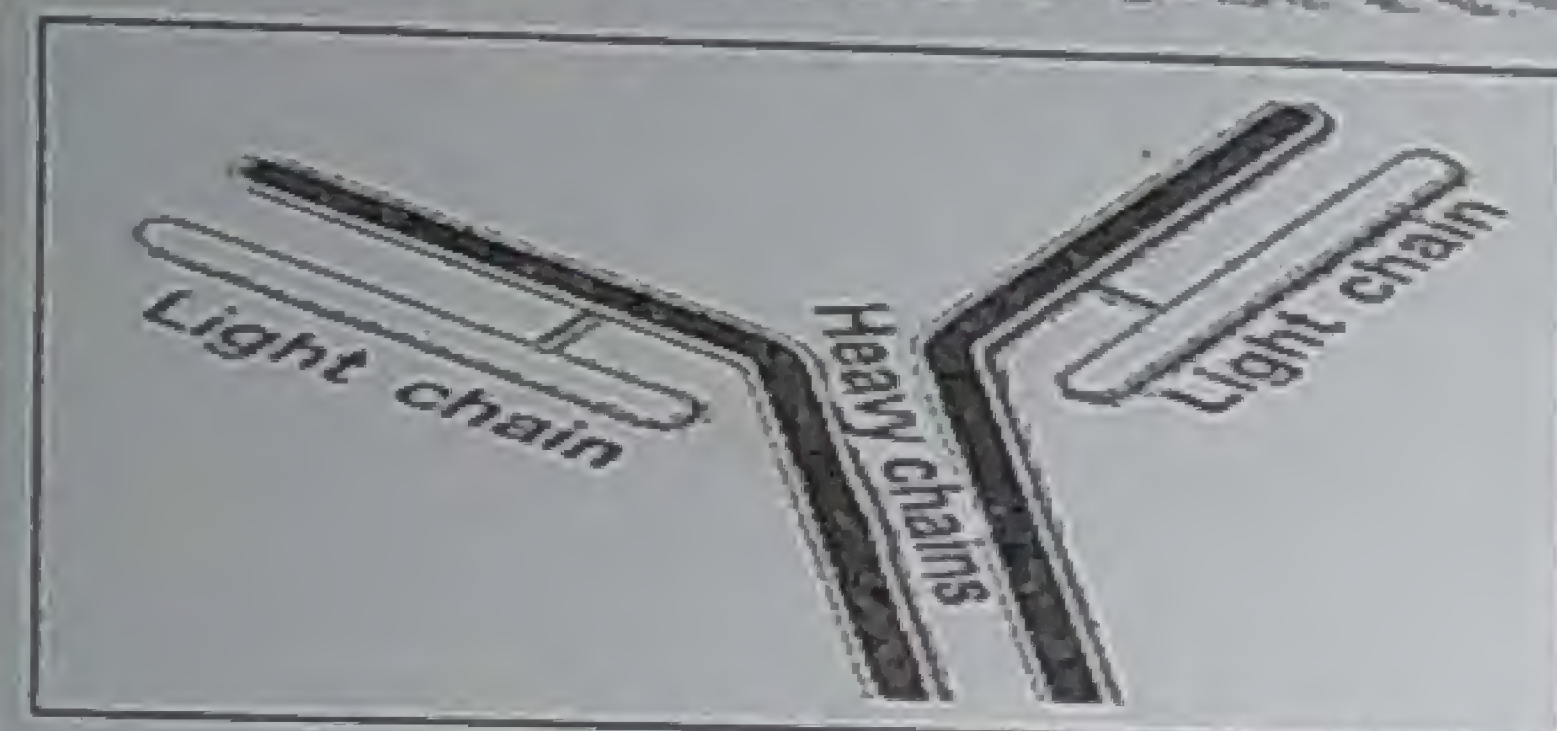
# Immunology 3

Humoral Immunity

Humoral Immunity



# Immunoglobulins (Ab)



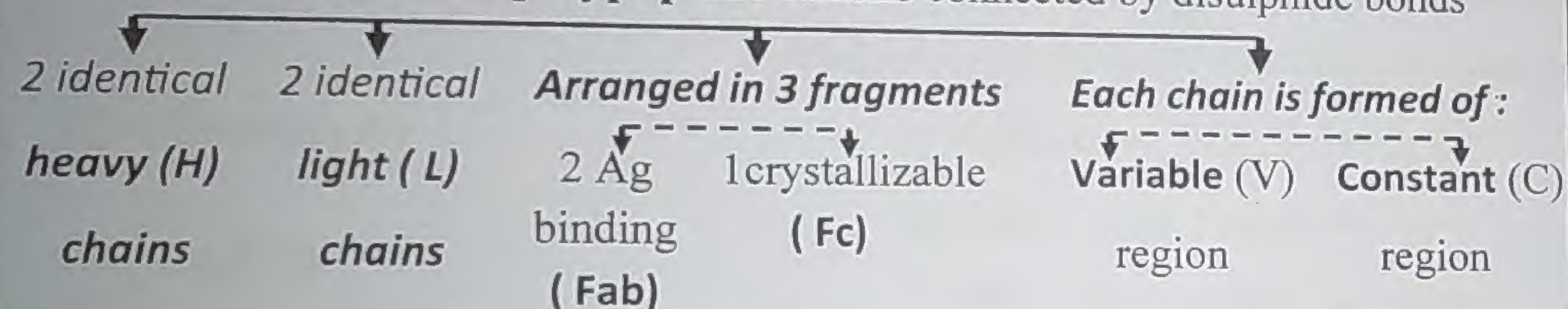
## Site

Glycoproteins found in all body fluids ( humors)

## Structure

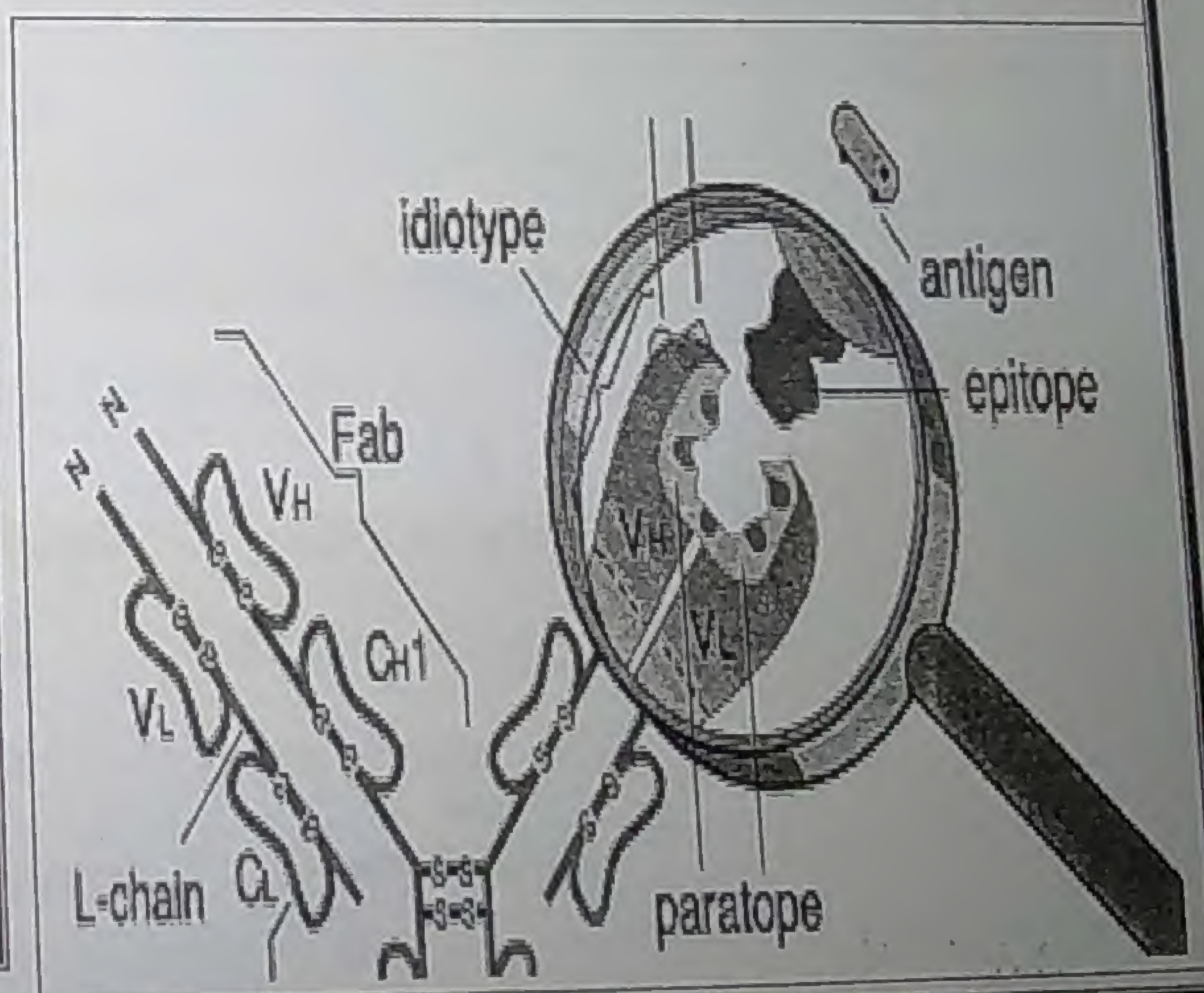
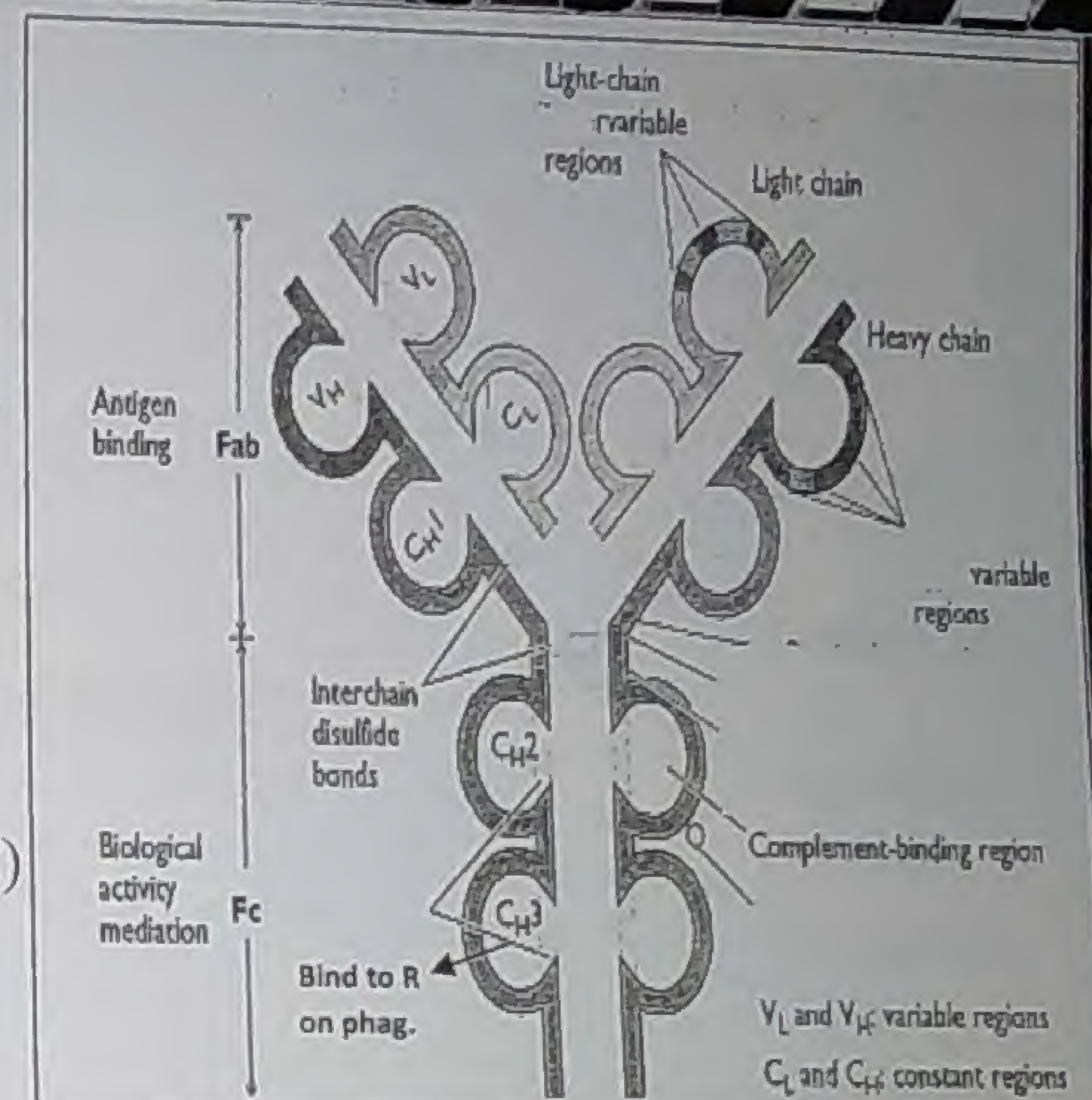
Each Ab molecule is Y shape

Formed of 4 polypeptide chains connected by disulphide bonds



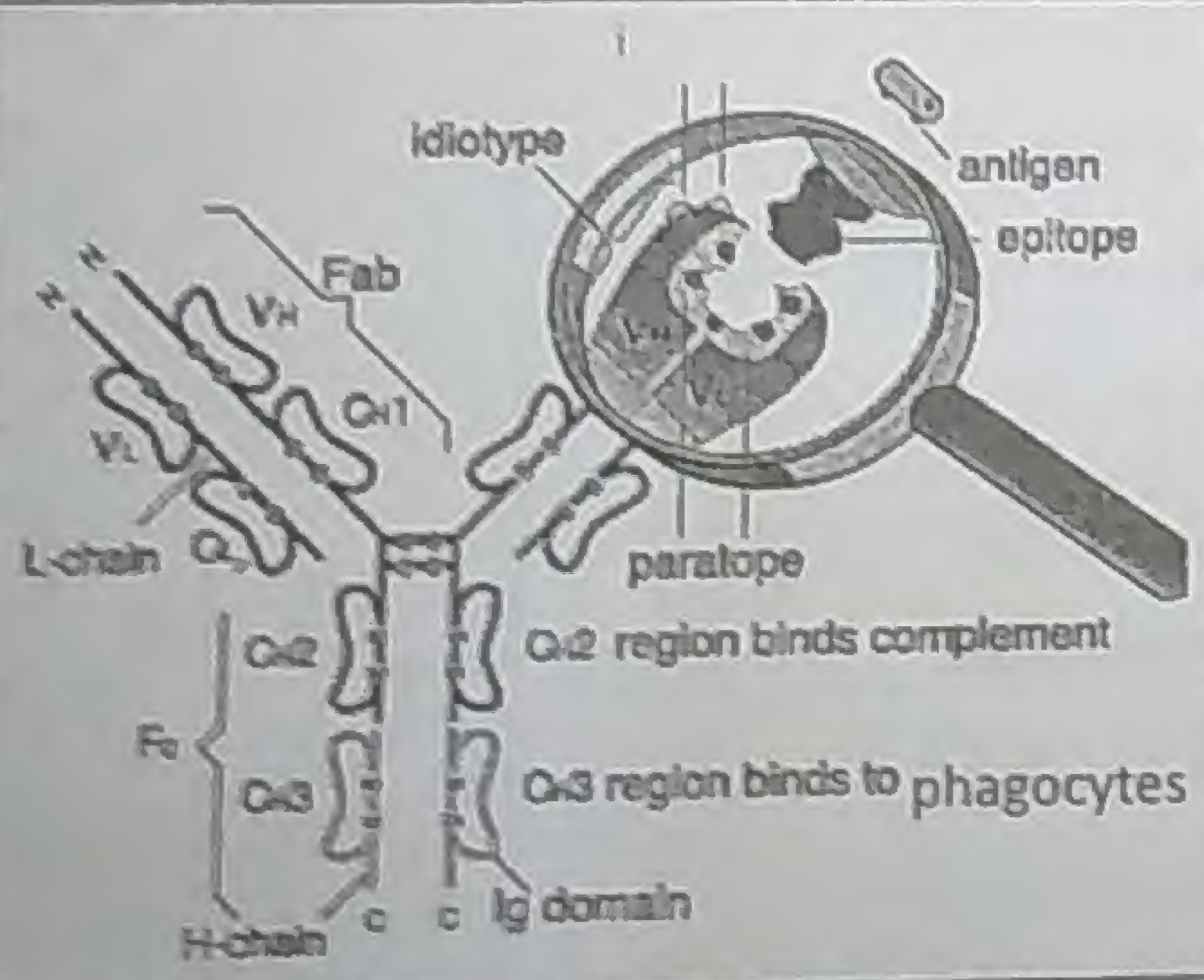
## Heavy and light chains

	Heavy (H) chain	Light (L) chains
I- Variable region	A- Site	
	Included in Fab	
	B-Structure	
	1 domain (VH )	1 domain (VL)
	C- Functions	
	<p>Forms the paratope or idiotypic of Ab</p> <p>Interacts specifically with the epitope of Ag (complementary to it)</p> <p>Each idiotypic is unique for 1 epitope &amp; produced by a specific clone of B cell</p>	





## II - Constant region

Heavy chain		Light chain		
A - Structure				
3 domains : CH1, CH2 & CH3		1 domain : CL		
B - Types				
<p>Change in a.a.sequence in CH region gives 5 types of H chains</p> <p>Classify Igs into <b>5 isotypes</b> ( classes)</p> <p>Each isotype is <b>named</b> according to <b>type of H</b> chain:</p> <ol style="list-style-type: none"> <li>1- Gamma ( <math>\gamma</math> ) chain <math>\rightarrow</math> Ig G</li> <li>2-Alpha ( <math>\alpha</math> ) chain <math>\rightarrow</math> Ig A</li> <li>3- Mu ( <math>\mu</math> ) chain <math>\rightarrow</math> Ig M</li> <li>4-Epsilon ( <math>\epsilon</math> ) chain <math>\rightarrow</math> Ig E</li> <li>5- Delta ( <math>\delta</math> ) chain <math>\rightarrow</math> Ig D</li> </ol>		<p>2 types :</p> <p>Kappa &amp; Lambda</p> <p>Found in all the 5 classes</p>		
 <p>The diagram illustrates the structure of an antibody. It shows two heavy chains (H-chain) and two light chains (L-chain) connected by disulfide bonds. The variable regions (V<sub>H</sub> and V<sub>L</sub>) are at the tips of the arms, while the constant regions (C<sub>H</sub>1, C<sub>H</sub>2, C<sub>H</sub>3) form the base. A Fab fragment is shown as one arm. A paratope is indicated on the variable region. A magnified view shows an antigen epitope binding to the paratope. Labels include: Idiotypic, antigen epitope, Fab, V<sub>H</sub>, V<sub>L</sub>, L-chain, C<sub>H</sub>1, C<sub>H</sub>2, C<sub>H</sub>3, H-chain, Ig domain, and C regions (C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>). Notes specify that the C<sub>2</sub> region binds complement and the C<sub>3</sub> region binds to phagocytes.</p>		<p><b>C - Functions</b></p> <p>Responsible for <b>biological functions</b> of different Igs (includes Fc)</p> <table border="0"> <tr> <td> <p>CH2 of IgM&amp;IgG</p> <p>Binding &amp; activation of complement</p> </td> <td> <p>CH3 of IgG</p> <p>Bind to receptors on phagocytes</p> <p><b>Opsonization</b></p> </td> </tr> </table> <p>No functions</p>	<p>CH2 of IgM&amp;IgG</p> <p>Binding &amp; activation of complement</p>	<p>CH3 of IgG</p> <p>Bind to receptors on phagocytes</p> <p><b>Opsonization</b></p>
<p>CH2 of IgM&amp;IgG</p> <p>Binding &amp; activation of complement</p>	<p>CH3 of IgG</p> <p>Bind to receptors on phagocytes</p> <p><b>Opsonization</b></p>			



# B lymphocytes

## Functions

Responsible for **humoral IR** by producing Abs

Eliminate EC microbes & their toxins

Professional APCs

⊕ Th cells

## Origin & Maturation

**BM** (no need for thymus)

## B cell receptor (BCR) complex

### A-Structure & Diversity

#### Structure

BCR : surface (membrane bound) IgM & IgD

V (variable) region recognizes specific epitope (complementary to it)

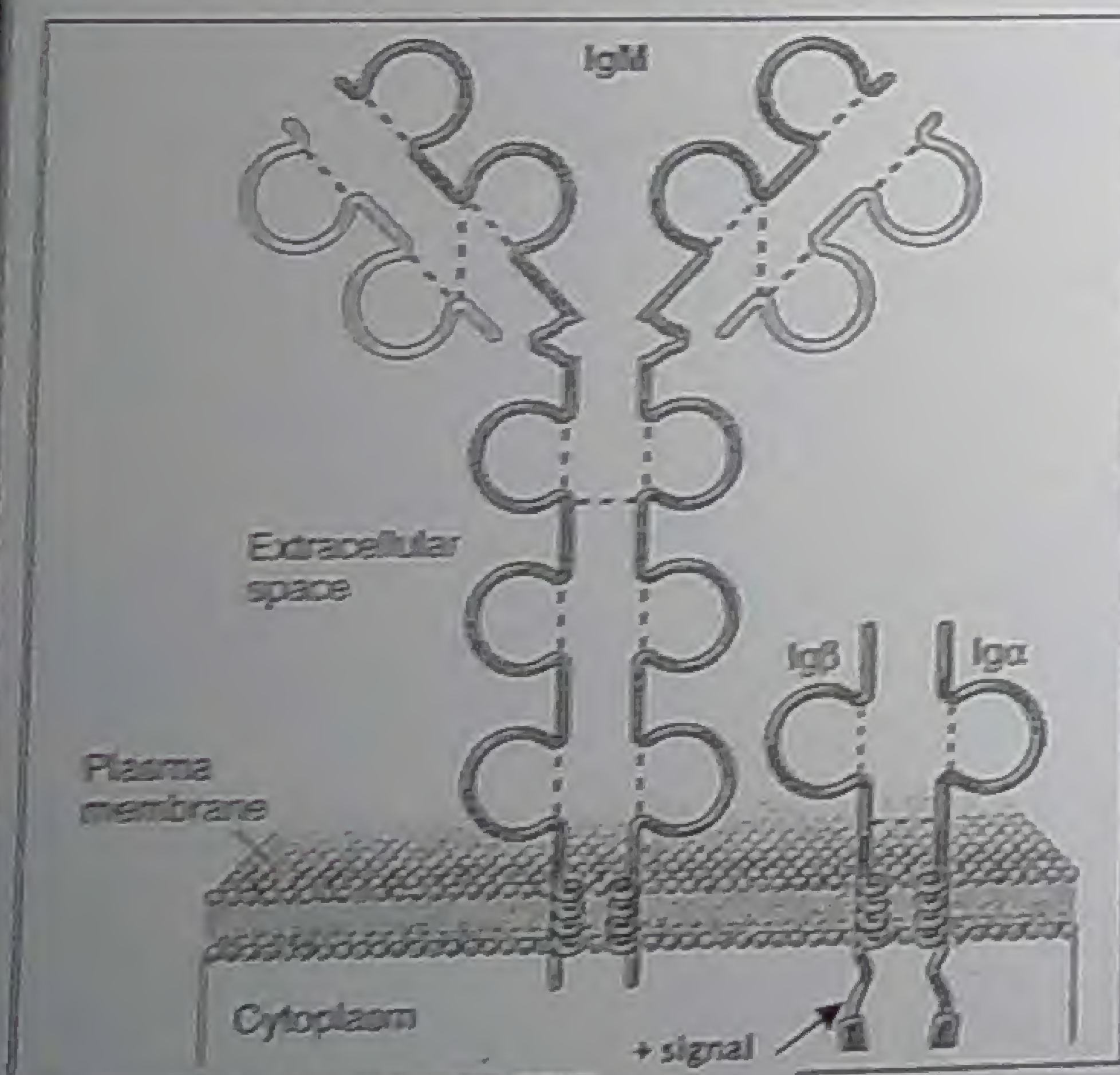
2 signaling mol.: Igα & Igβ

Transmit IC activation signal

#### Diversity

Millions of B cells exist

React with millions of different peptides



## B-Negative selection

B cells expressing BCR that can react with **self peptides** (self reactive cells) are killed by **apoptosis** (clonal deletion)

### Self tolerance

No autoimmune reactions

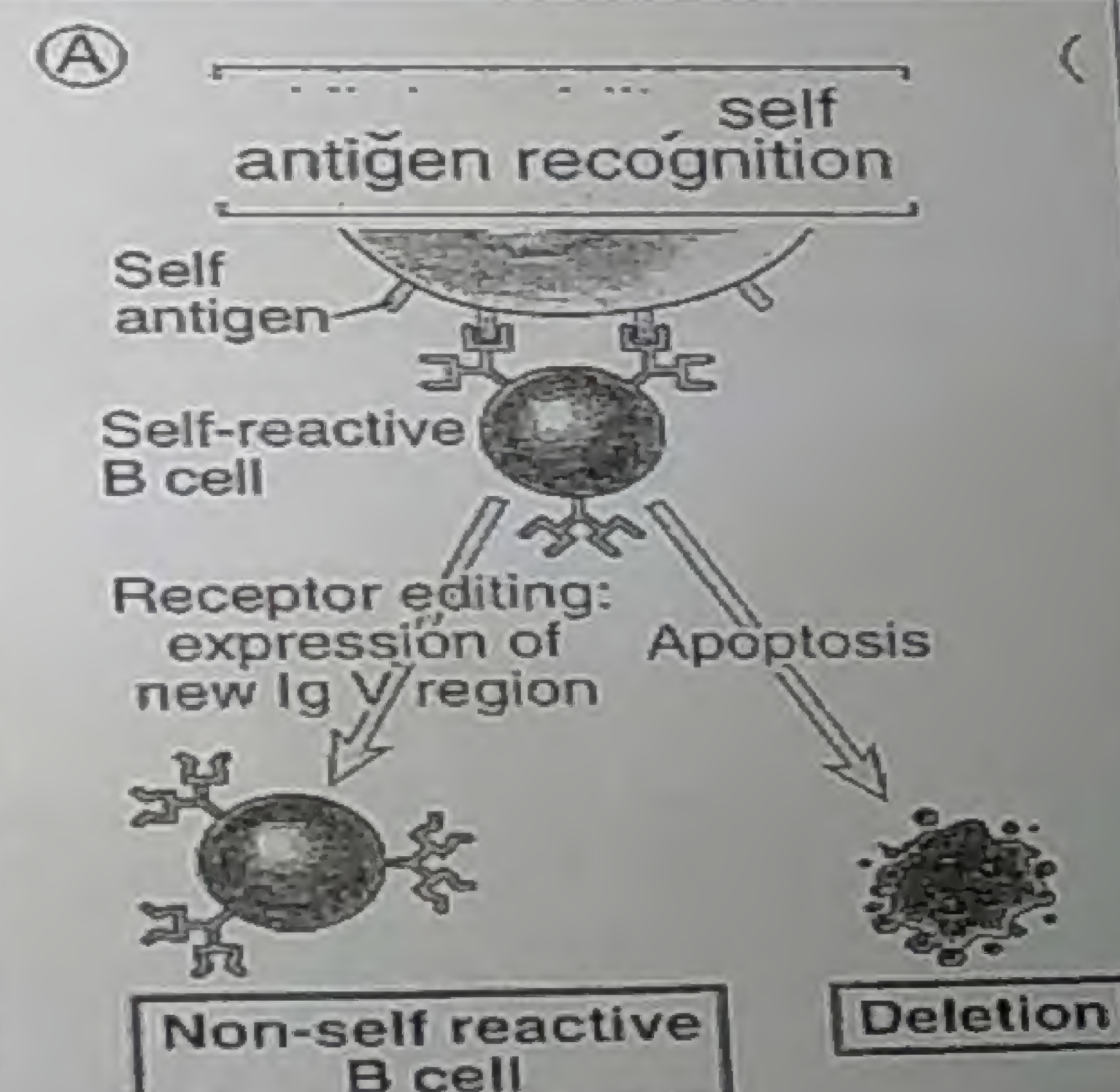
## Release & Sites

Mature B cell circulate in blood

(30% of small lymphocytes)

& the remaining are T lymphocytes

2<sup>ry</sup> lymphoid organs : LNs, spleen & GALT

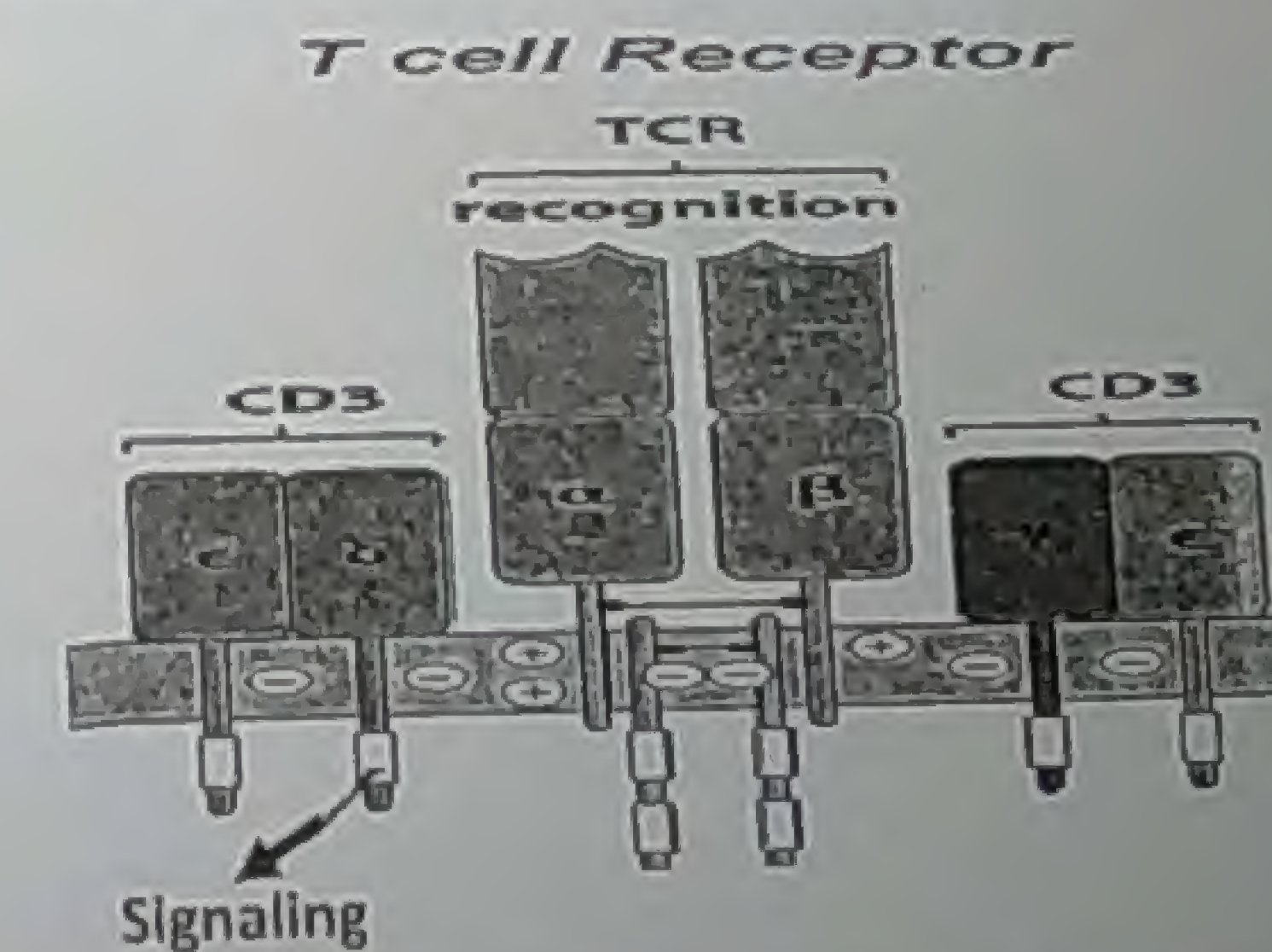
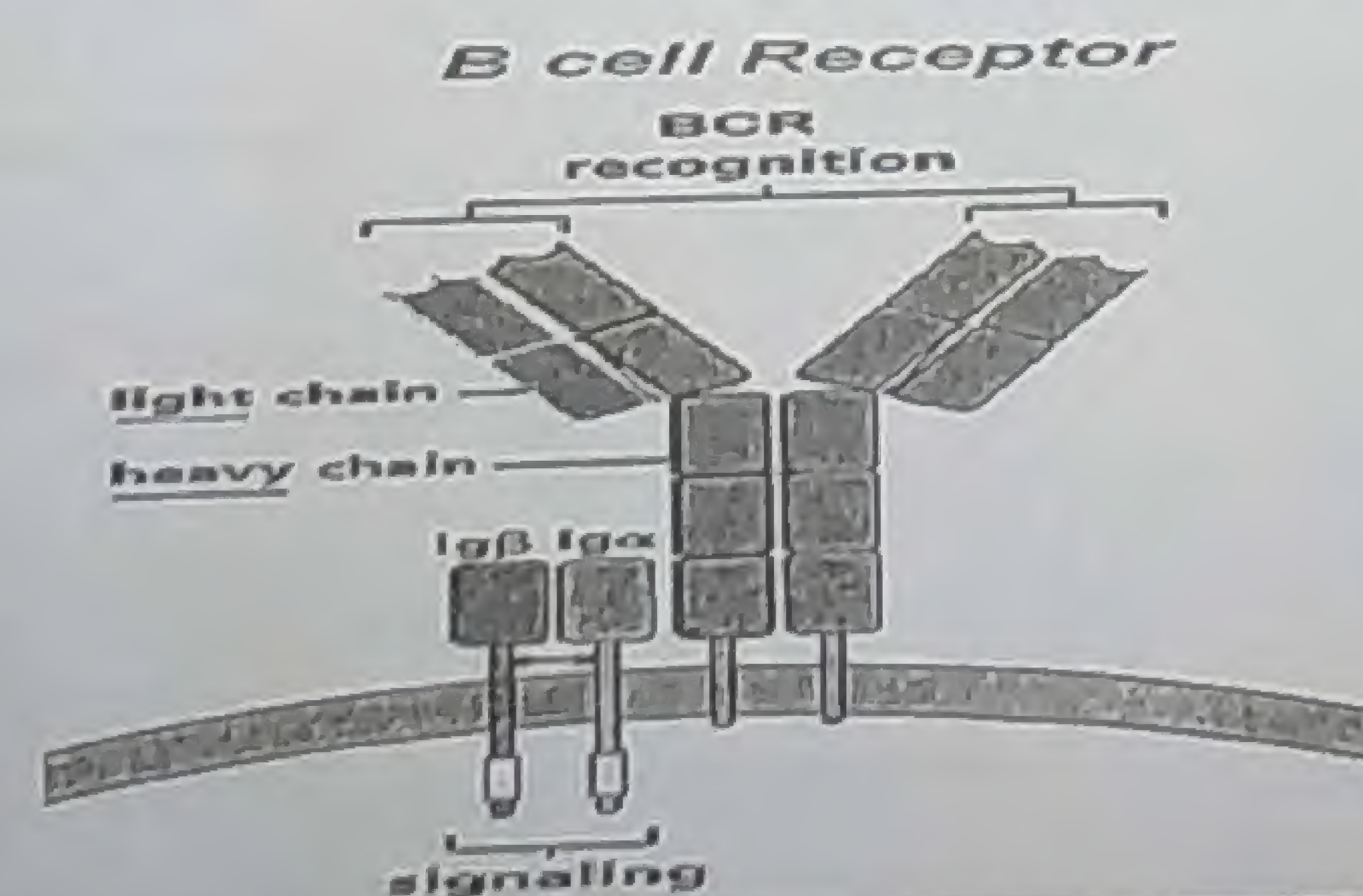




## Comparison between B cell and T cell receptor

	B cell receptor	T cell receptor
	BCR complex	TCR complex
1-Structure	i. Membrane bound <i>IgM</i> & <i>IgD</i>  ii. Signal transducing molecule <i>Ig α</i> & <i>Ig β</i>	i. 2 polypeptide chains: $\alpha$ & $\beta$  CD3
2-Ag recognition	By <i>V</i> regions of <i>H</i> & <i>L</i> chains of membrane bound Igs	By <i>V</i> regions of $\alpha$ & $\beta$ chains
3-MHC restriction	No Recognize Ag <i>without MHC proteins</i>	Recognize Ag only in association with MHC proteins
4-Ag characters	i. Free (soluble) ii. Proteins iii. Lipids, polysaccharides, nucleic acids iv. Small chemicals e.g drugs	i. On APCs ii. Proteins
5-Secreted form	Yes <i>Pentameric IgM</i> is present in serum	No (always membrane bound)

### T Cell and B Cell Antigen Receptors (TCR and BCR)

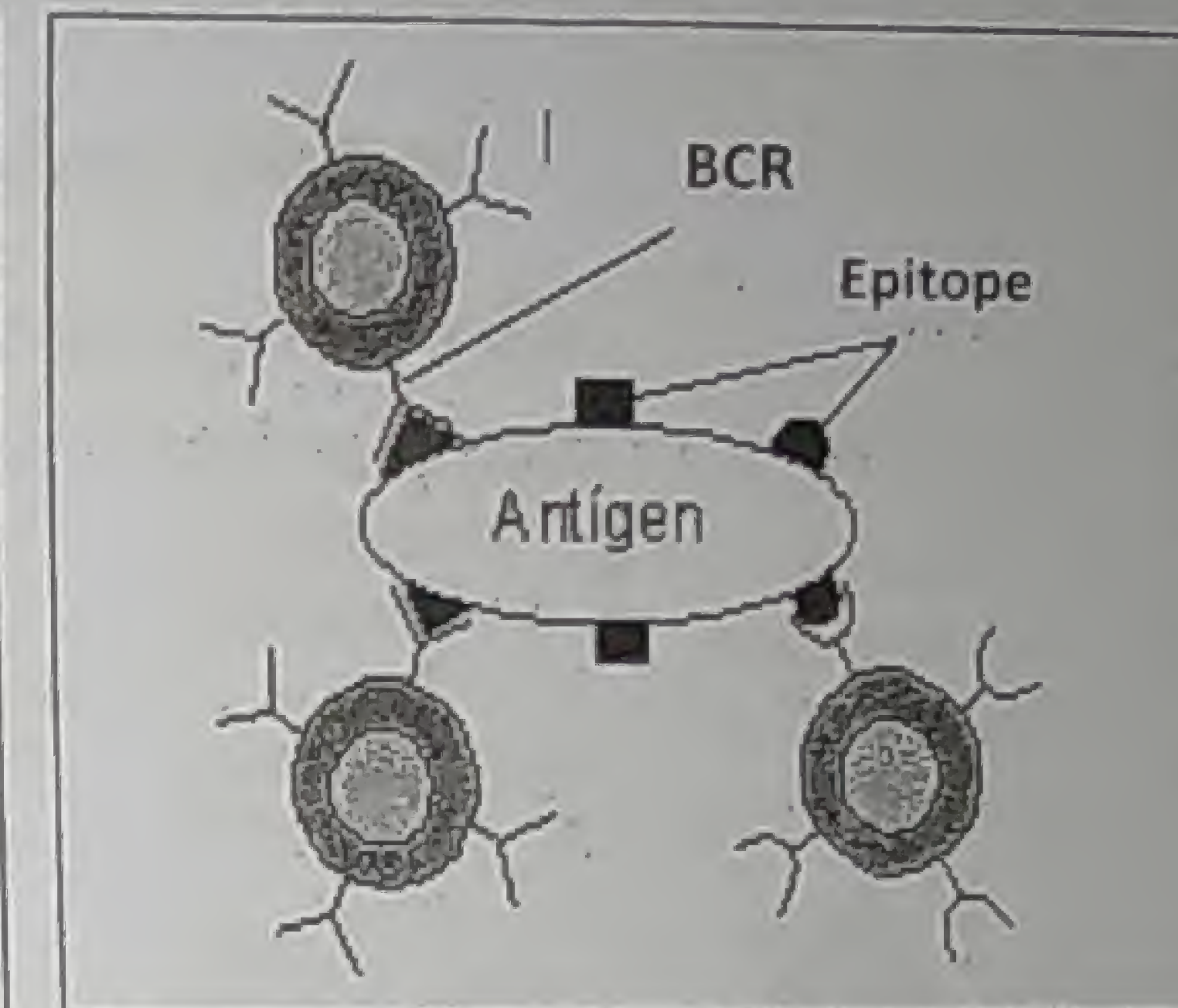
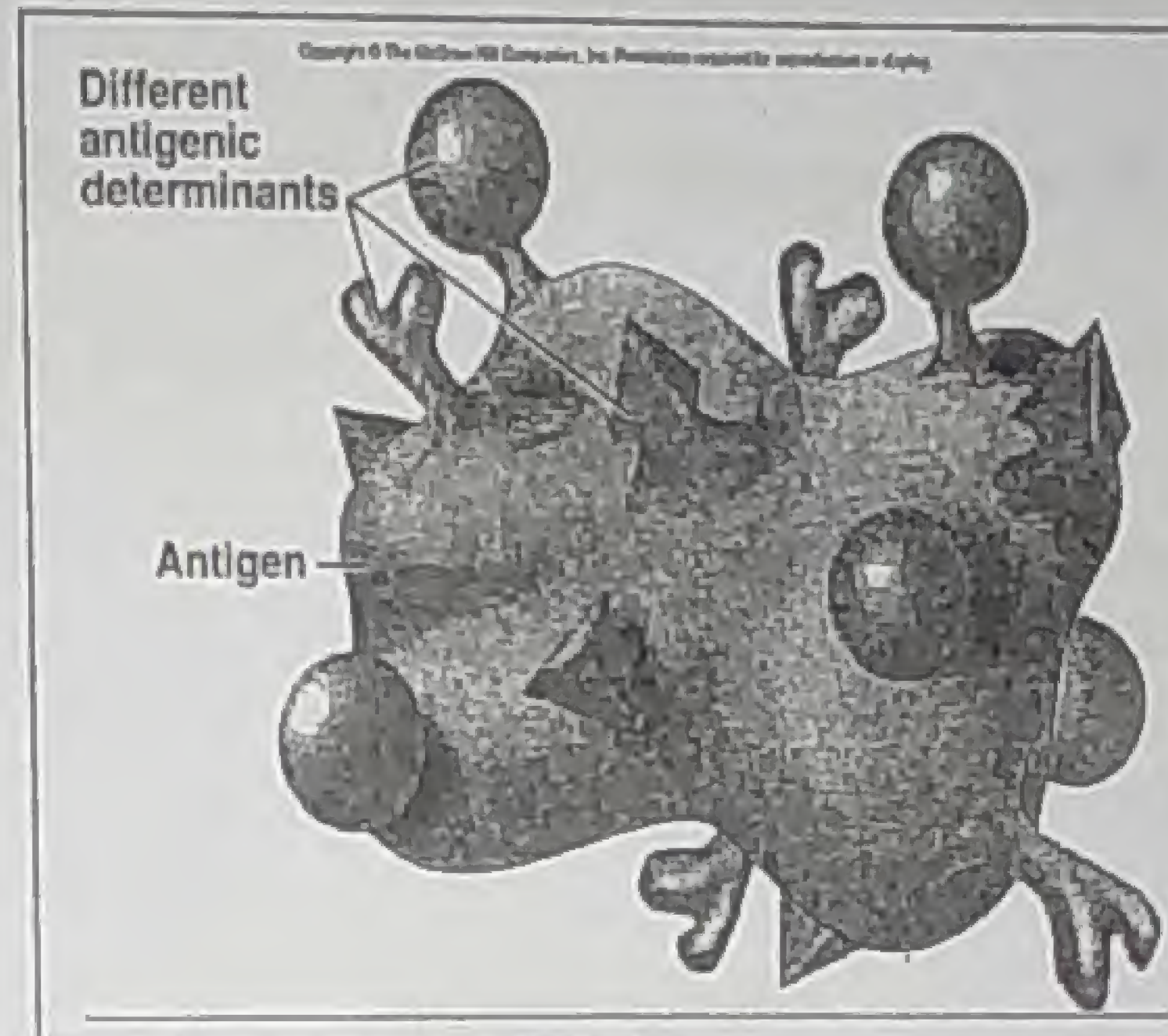
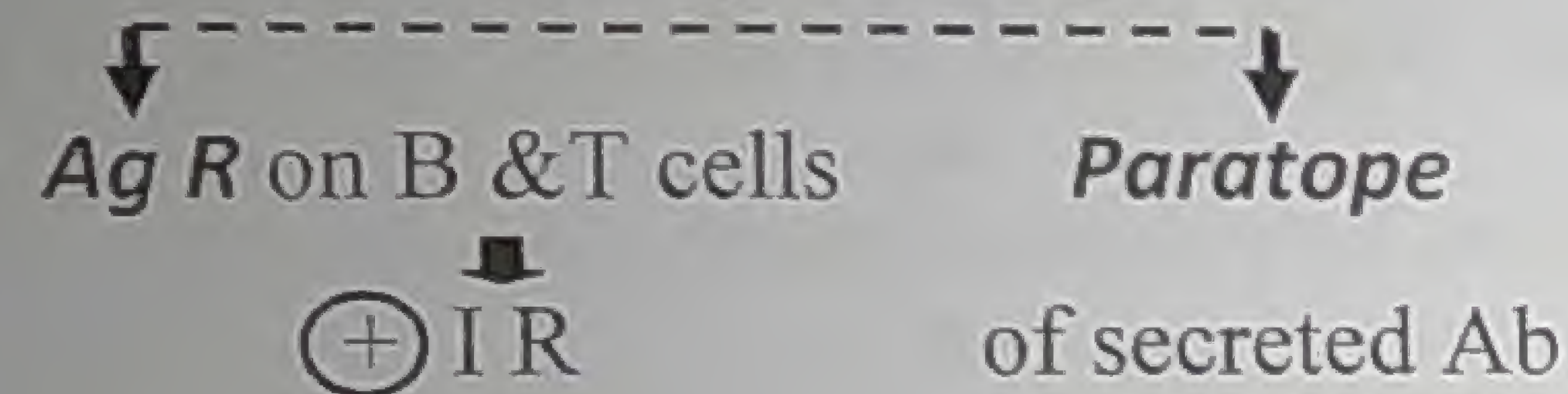




# Epitope ( antigenic determinant)

## Size & Function

Is the smallest biochemical unit of Ag  
that binds specifically with



## Types

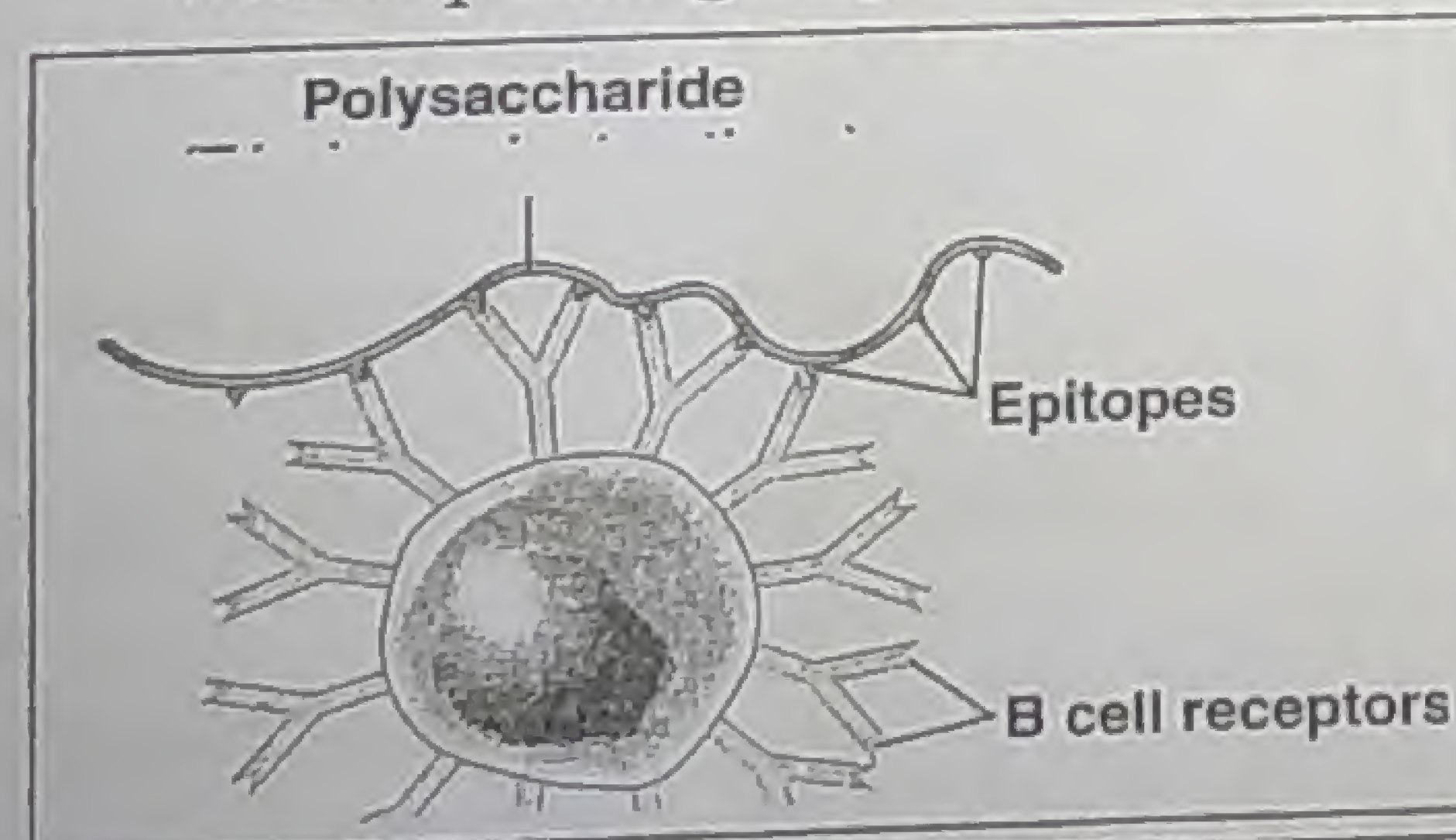
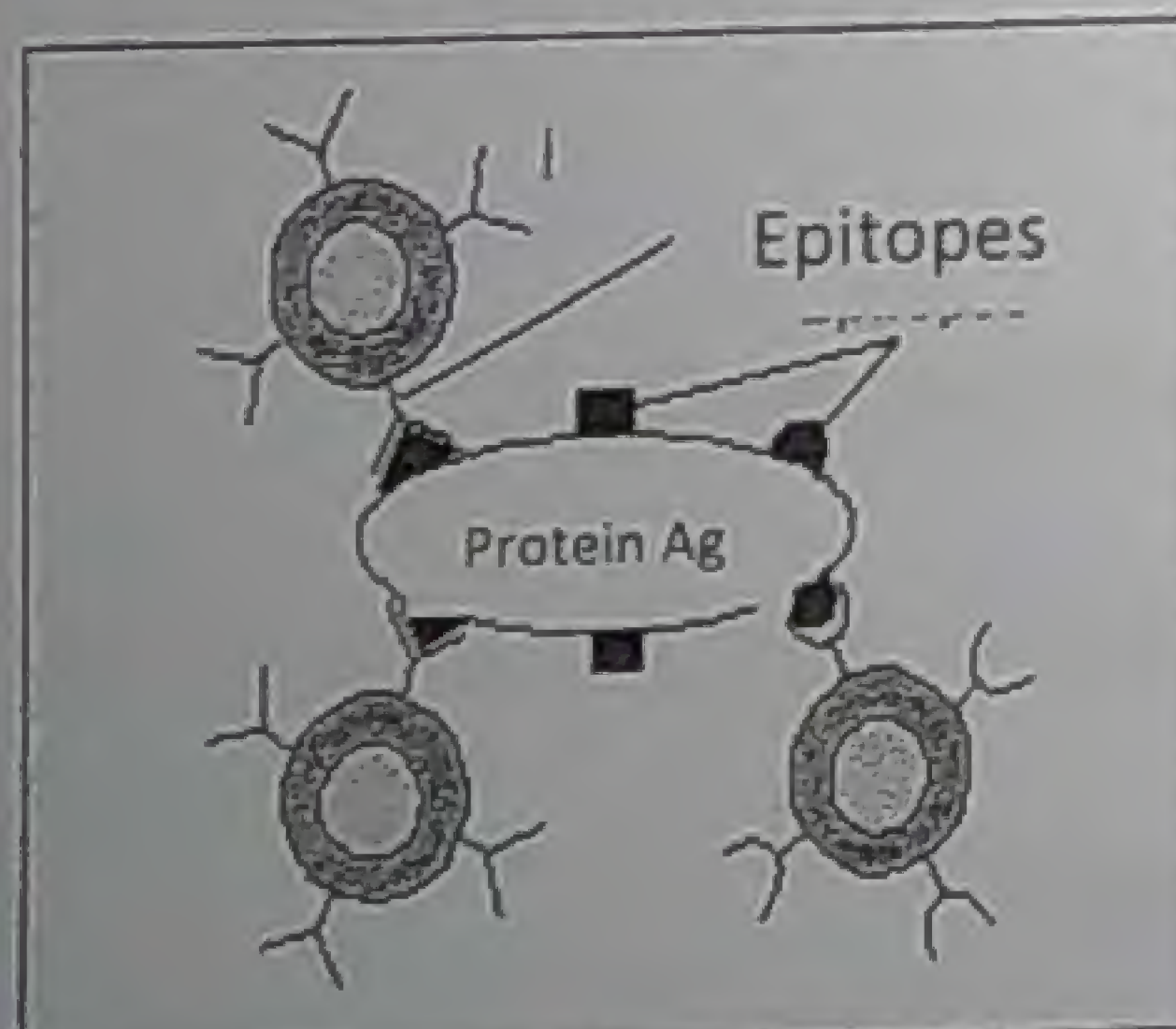
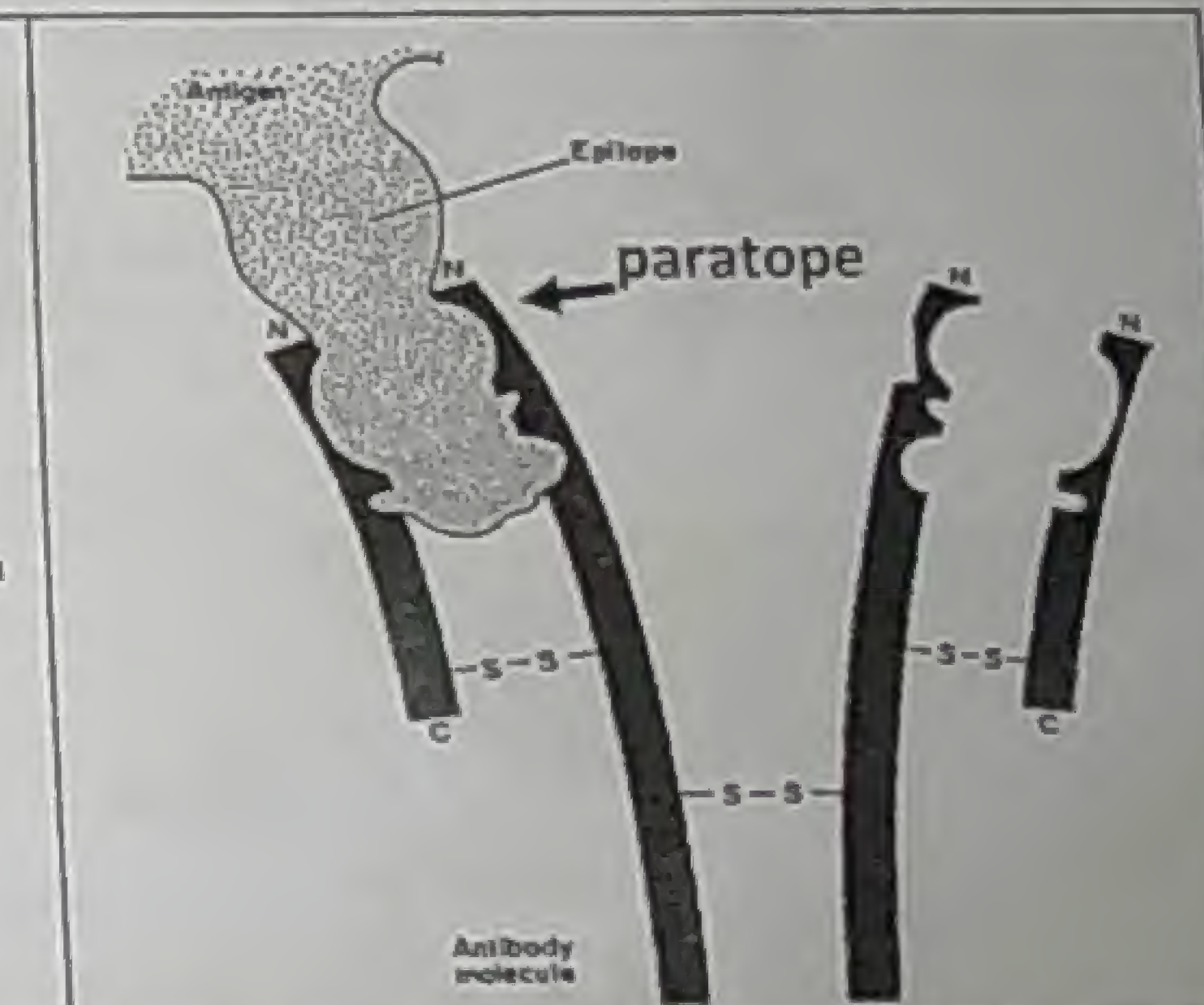
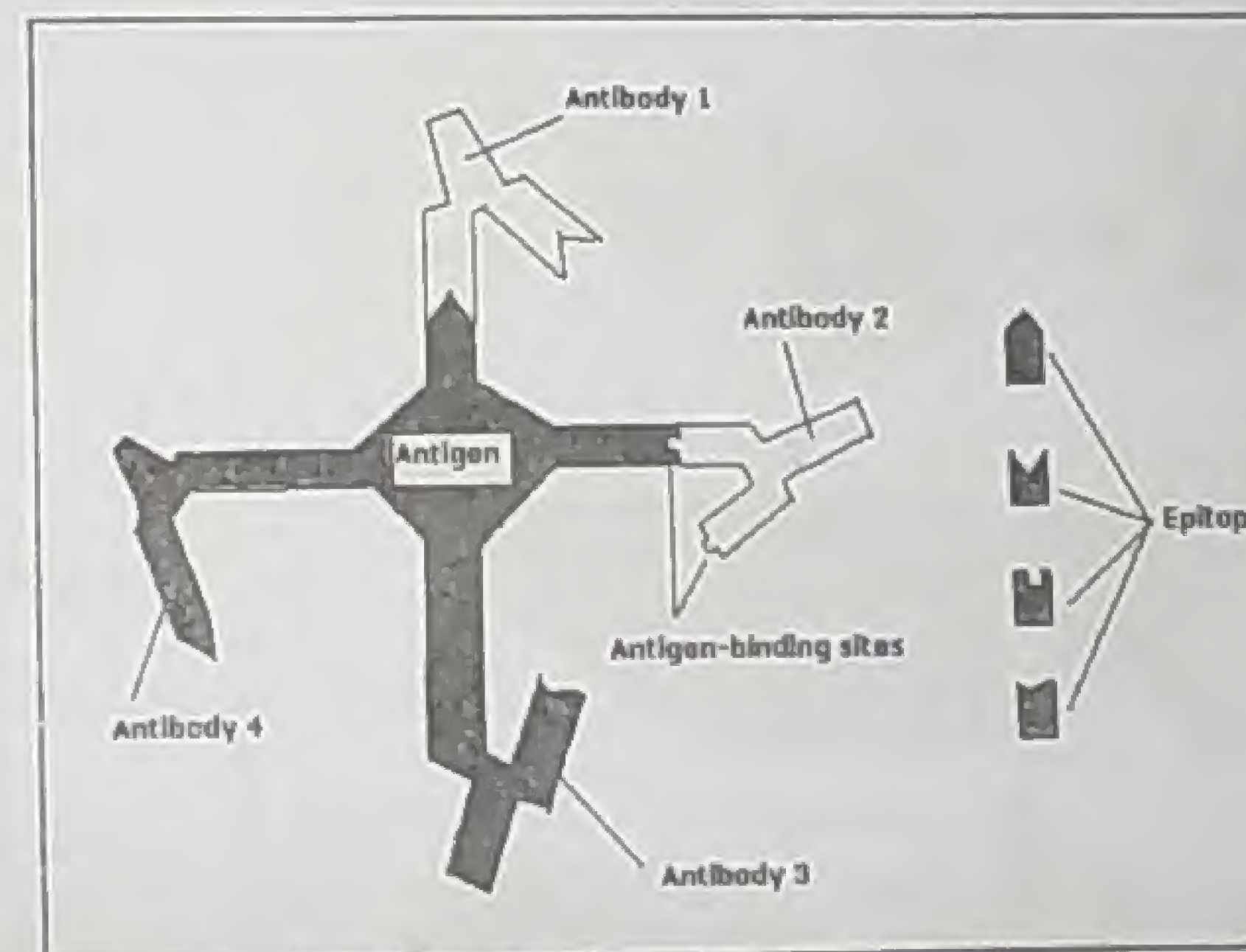
1 Ag may have

Several *different*  
epitopes

e.g protein Ag

Several *identical*  
epitopes

e.g CHO (polysaccharide)  
with repeating sugars





# Activation of B cells

## I-Protein Ags: T (thymus) dependent Ags

Need of T helper cells to activate B cells → B cells will act as APCs to Th

### 1-Ag binds to BCR (IgM & IgD)

Internalized (receptor mediated endocytosis)

Processed & associated with MHC II proteins

Displayed on the surface

### 2-Activation of Th cells

Peptide – MHC class II bind

B7 binds

TCR/CD3 complex & CD4

CD28(Costimulation)

Cytokines production

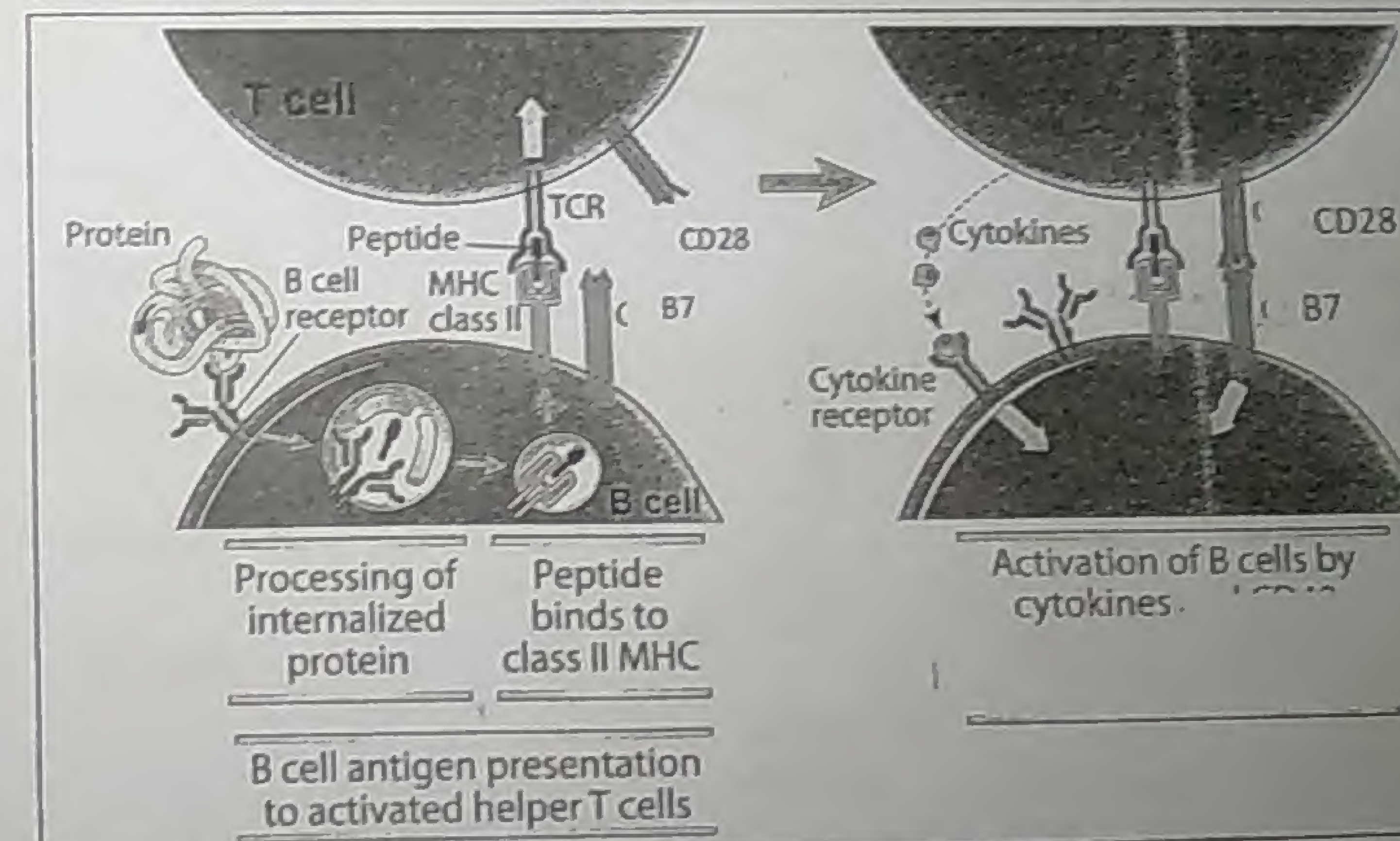
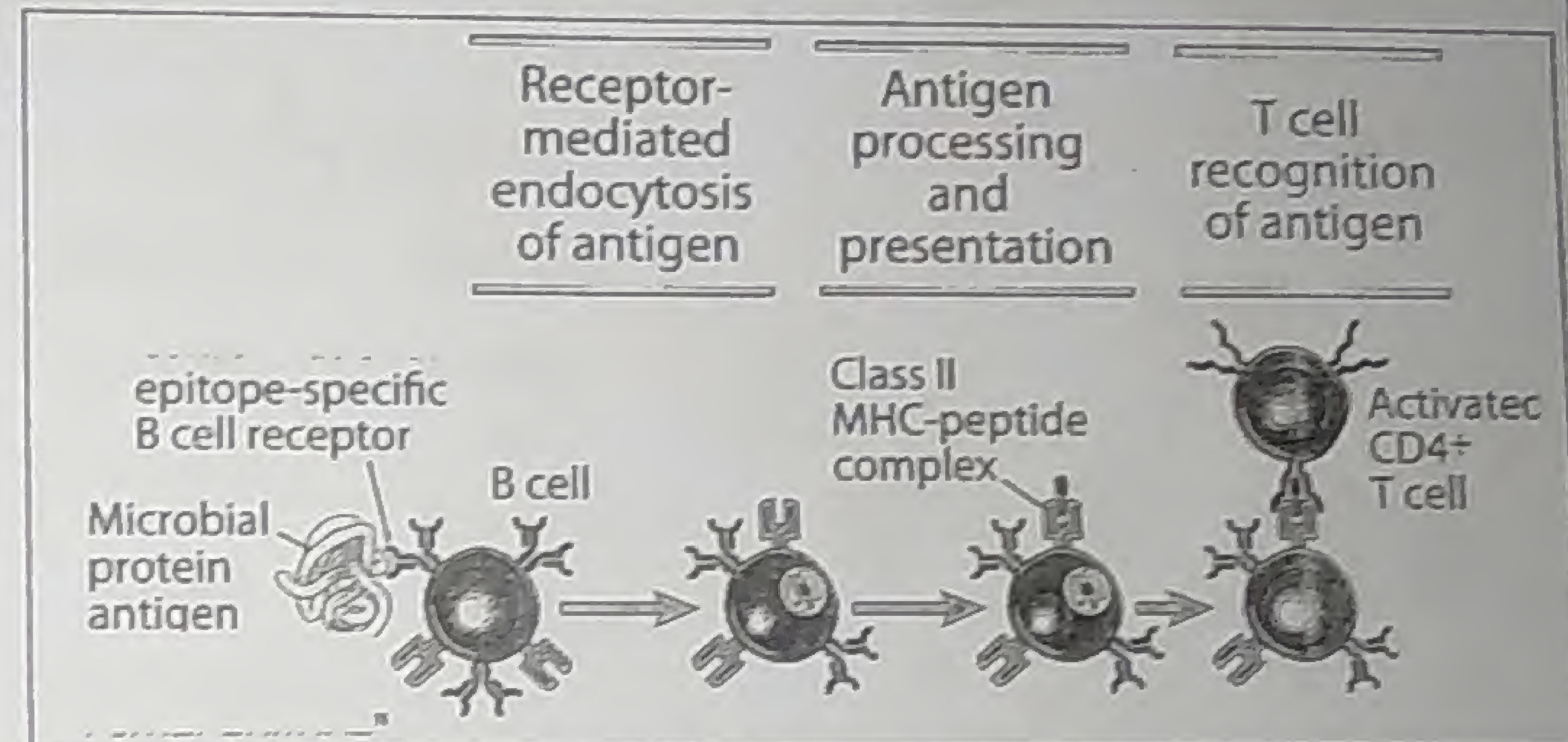
IL2, IFN $\gamma$  (Th1)

IL4, 13, 5, 6 & 10(Th2)

### 3-Cytokines activate B cells

Proliferation into clone of cells with *same Ag specificity*

Clonal expansion





#### 4-Differentiation of activated B cells into

##### A-Plasma cells

##### 1-Effector functions

Produce thousands  
of Ab mol./ sec  
specific  
for epitope  
Die after  
few days

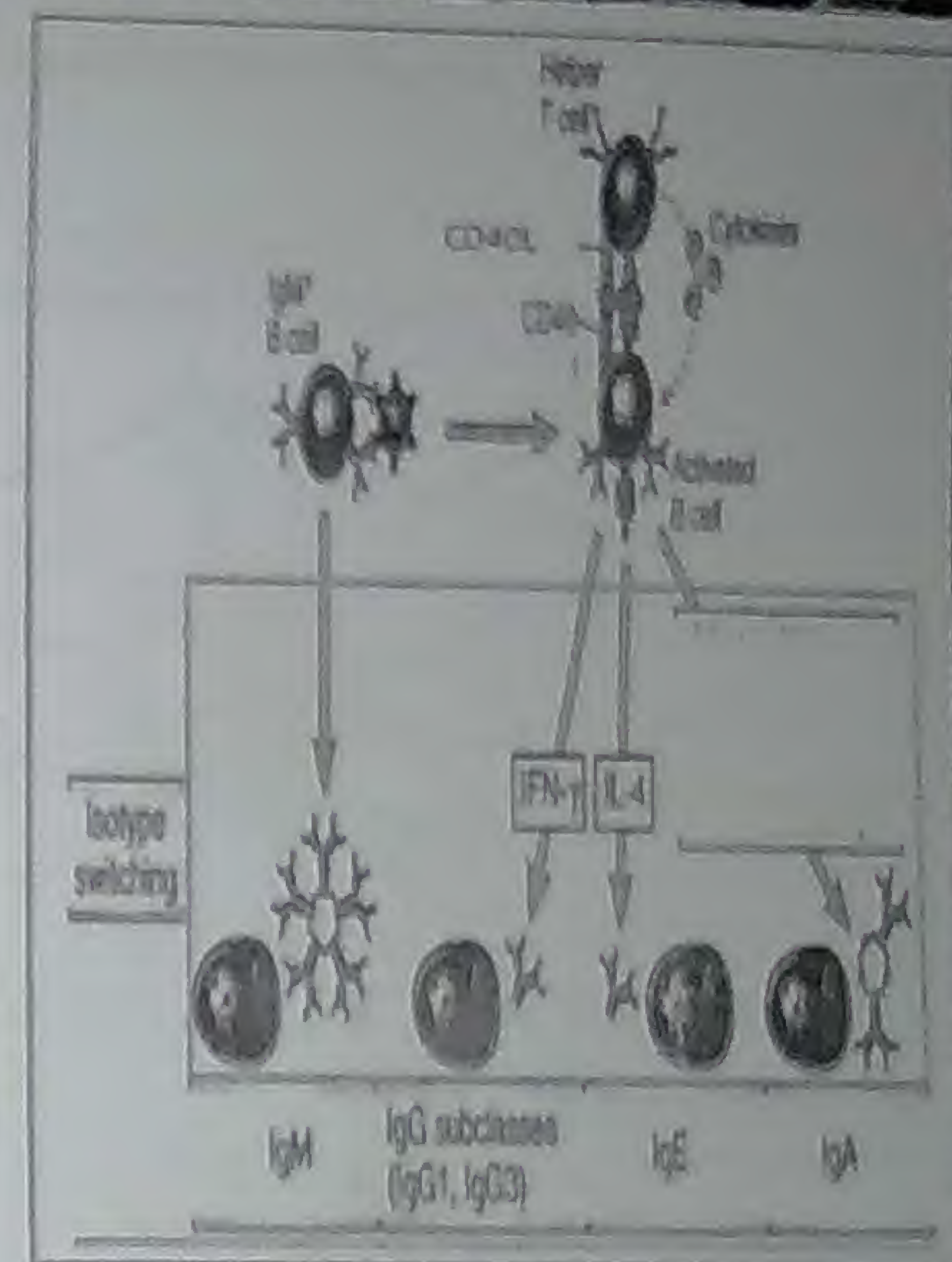
##### 2-Ab production

1<sup>st</sup>  
Produce  
IgM  
(secreted)

##### Isotype ( class ) switch

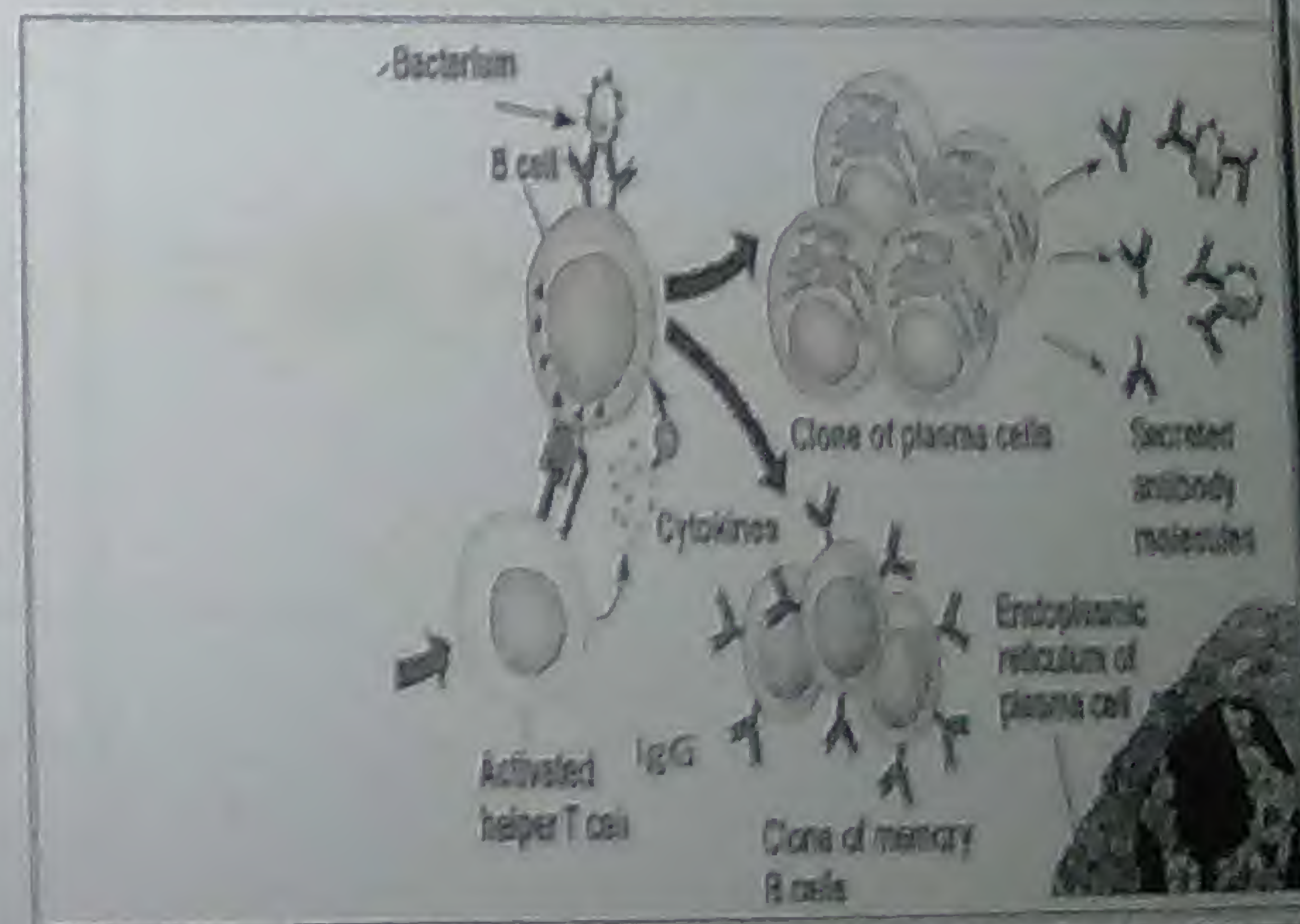
Is a change  
in the H chain  
Production of another  
class of Ab  
while maintaining  
the same  
Ag specificity

Requires 2 signals  
CD40 L on  $\oplus$  T cells  
Binds to  
CD40  
on B cells  
Cytokines  
• IFN $\gamma$   
IgG1&3  
• IL4&13  
IgE



##### B-Memory cells

Remain	Express	Activated	Stimulated	Rapid &
quiescent	surface IgG <i>Replaces IgM, D</i>	rapidly	by	Strong
for long	Ag receptor	upon	cytokines	production
periods		reexposure	from	of Abs
		to same Ag	memory Th	



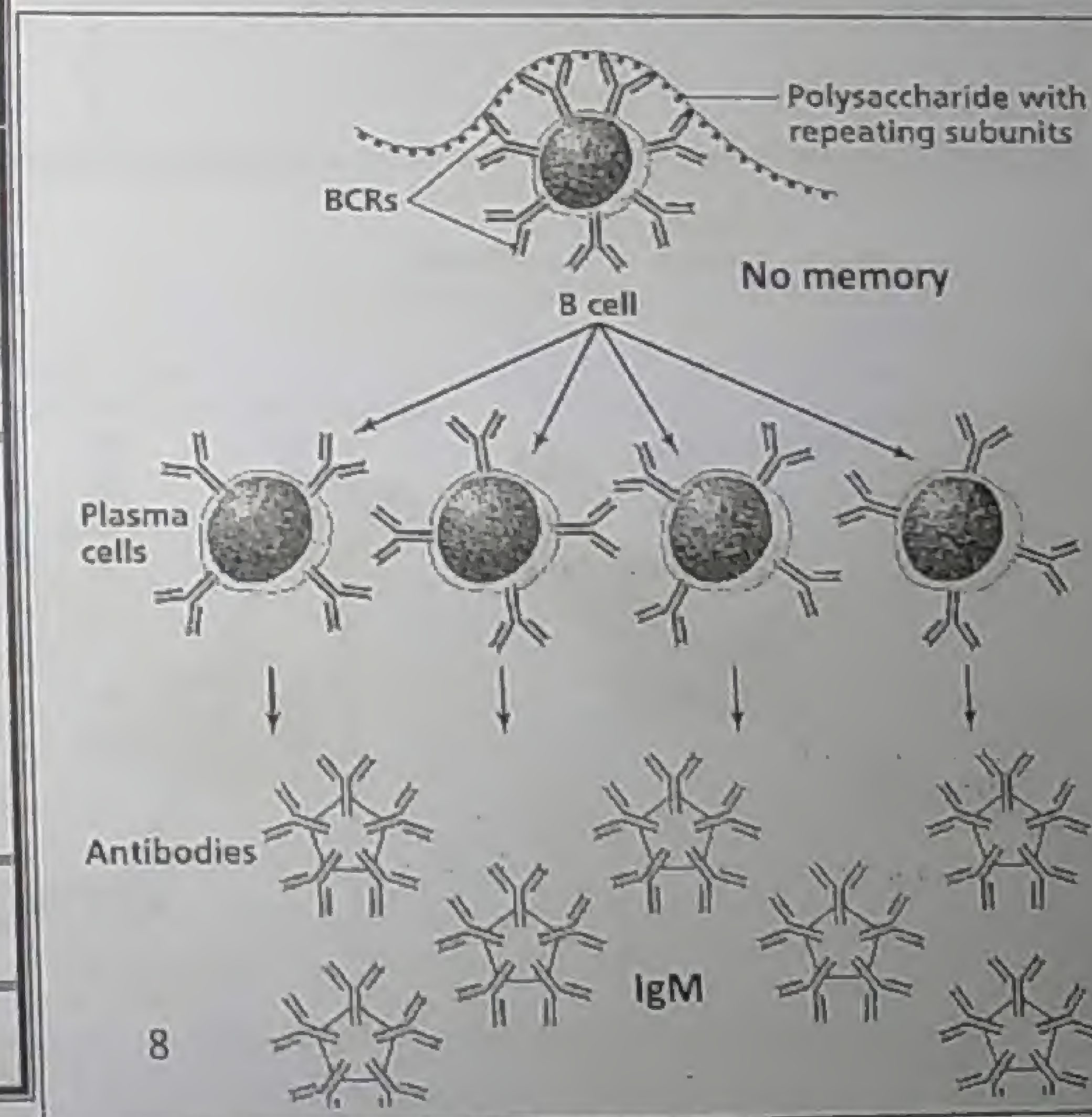
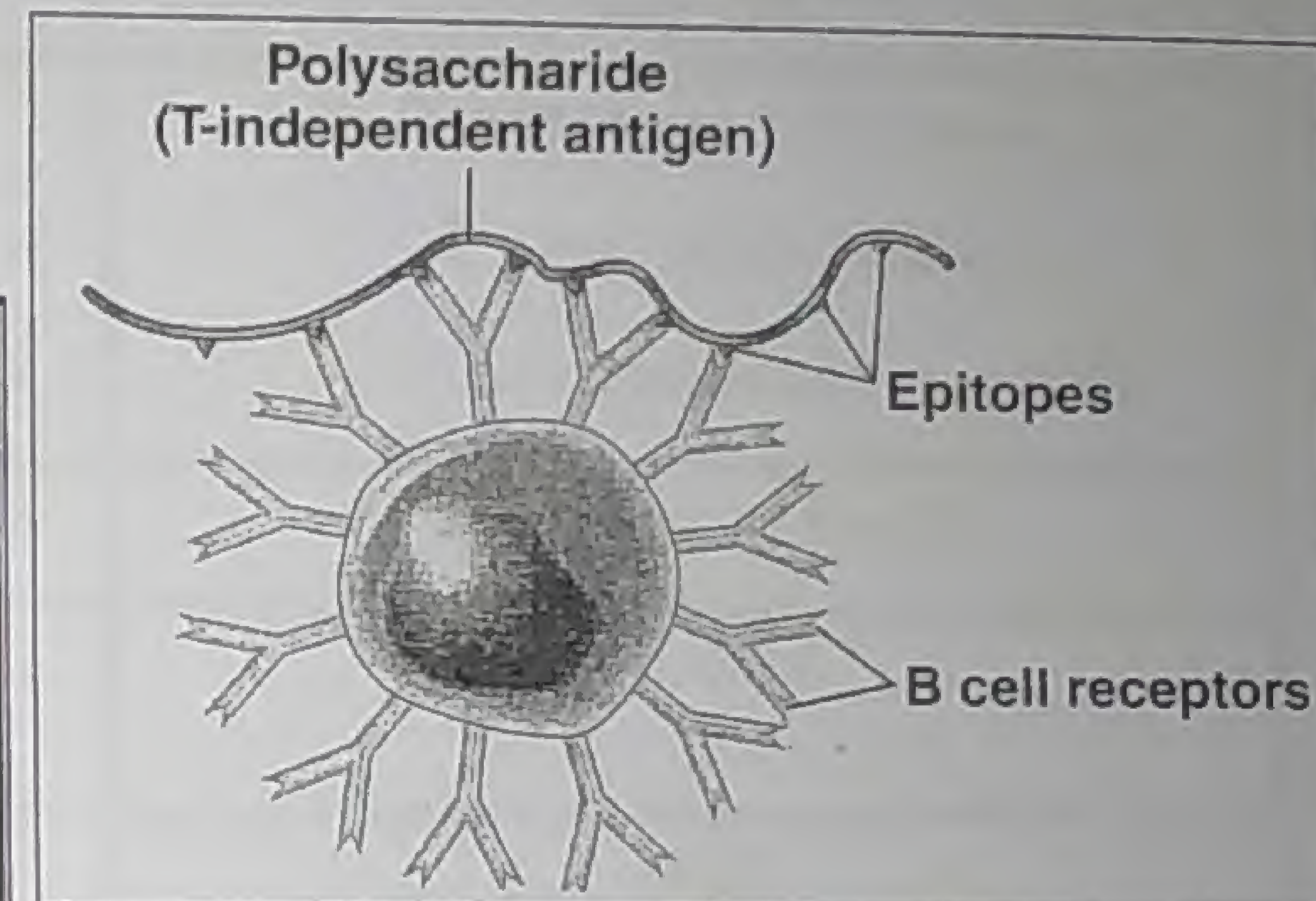


## II-Polysaccharide Ags : T ( Thymus ) independent Ags

Activate B cells directly

↓  
No need for Th

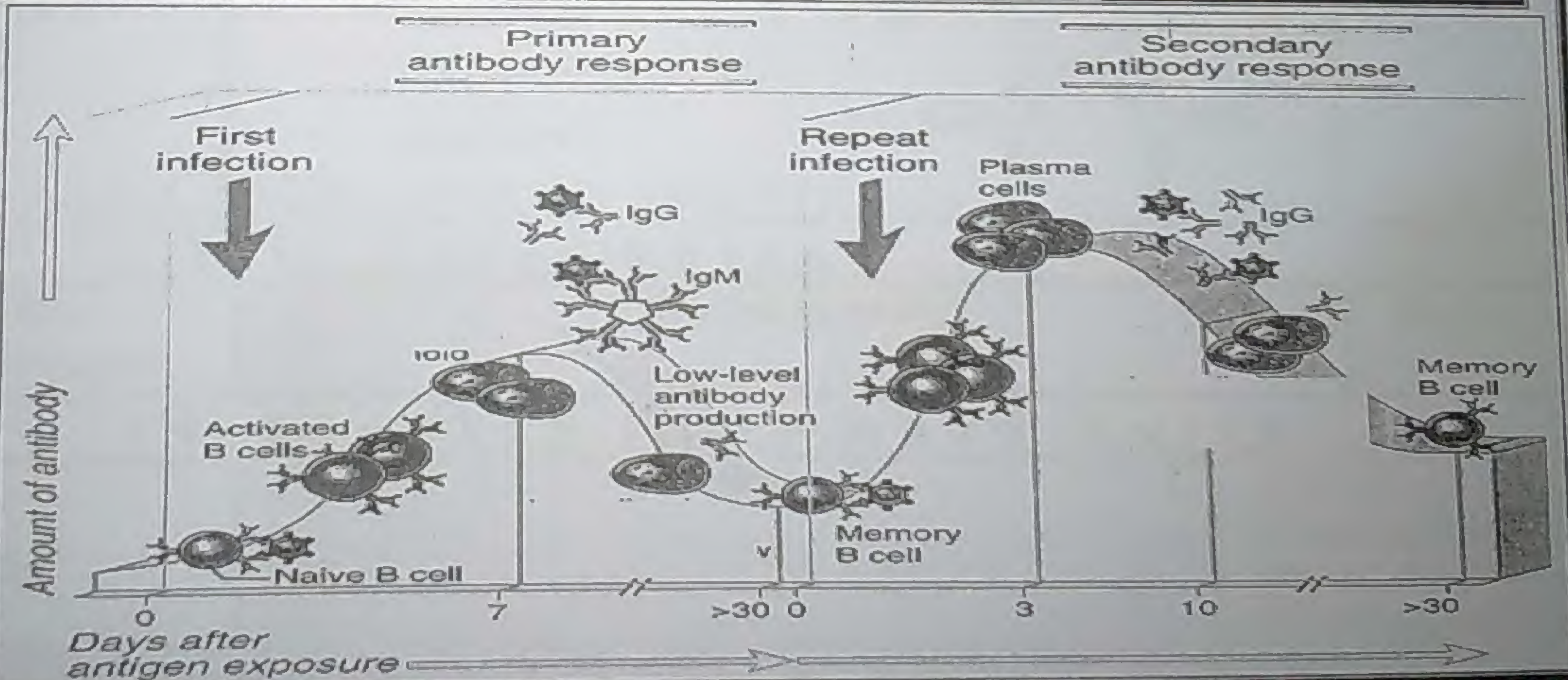
☆	T cell dependent Ags	T cell independent Ags
1- Structure & Examples	Not formed of repeating epitopes e.g • Proteins • Foreign RBCs • Hapten-carrier conjugate	Formed of <i>repeating multiple epitopes</i> e.g Bacterial polysaccharides (capsule)
2- Characters of IR	i. Need ⊕ of Th cells ( B cell acts as APC )	i. Activate B cells directly <i>faster response</i> ( No need for Th )
	ii. Isotypes of produced Abs	
	IgM + IgG, A & E ( Isotype switch )	IgM only ( No isotype switch due to absence of: IFN $\gamma$ , IL4 & 13 )
	iii. Memory ( <u>anamnestic</u> ) response	
	Present	No





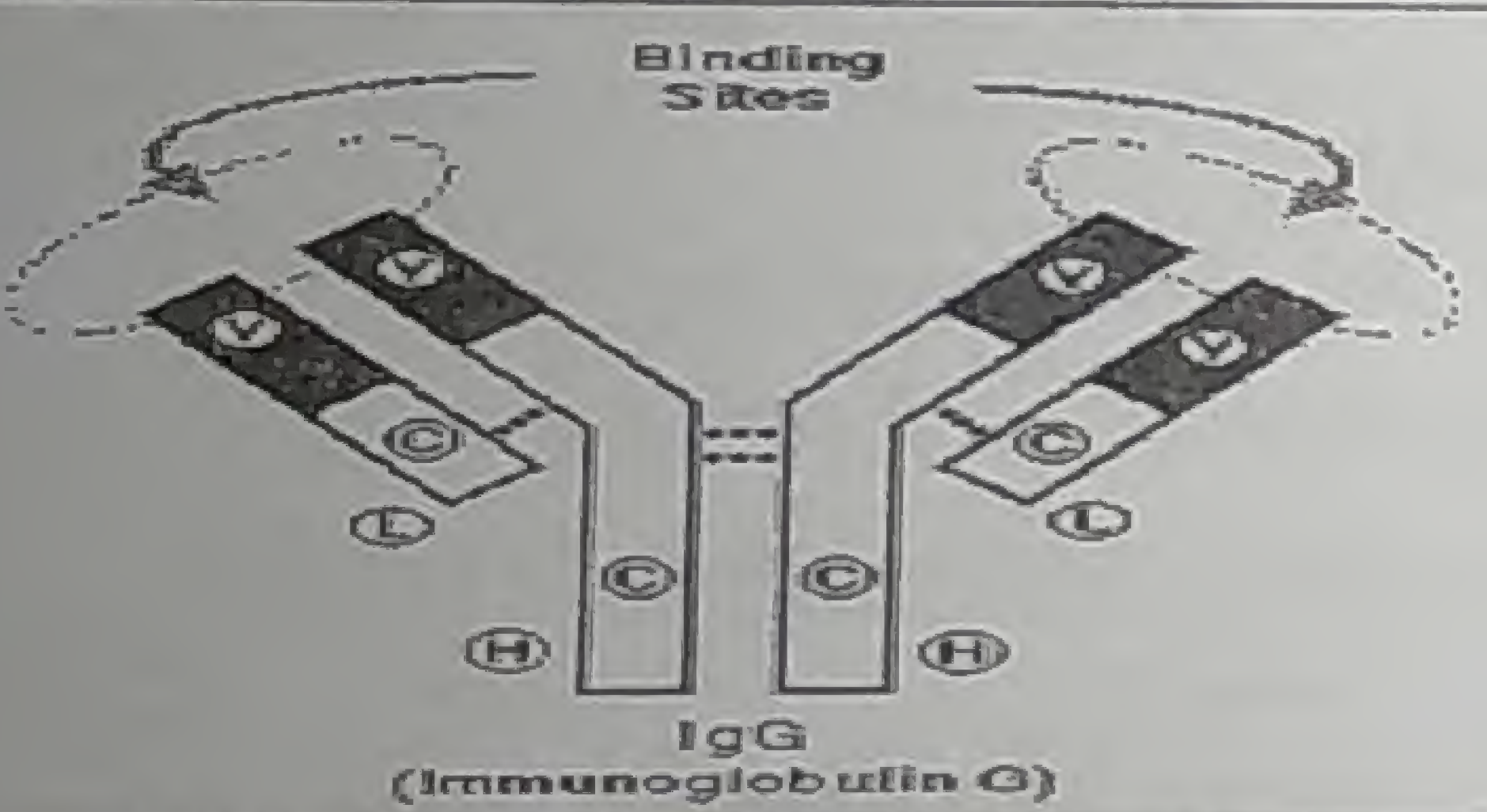
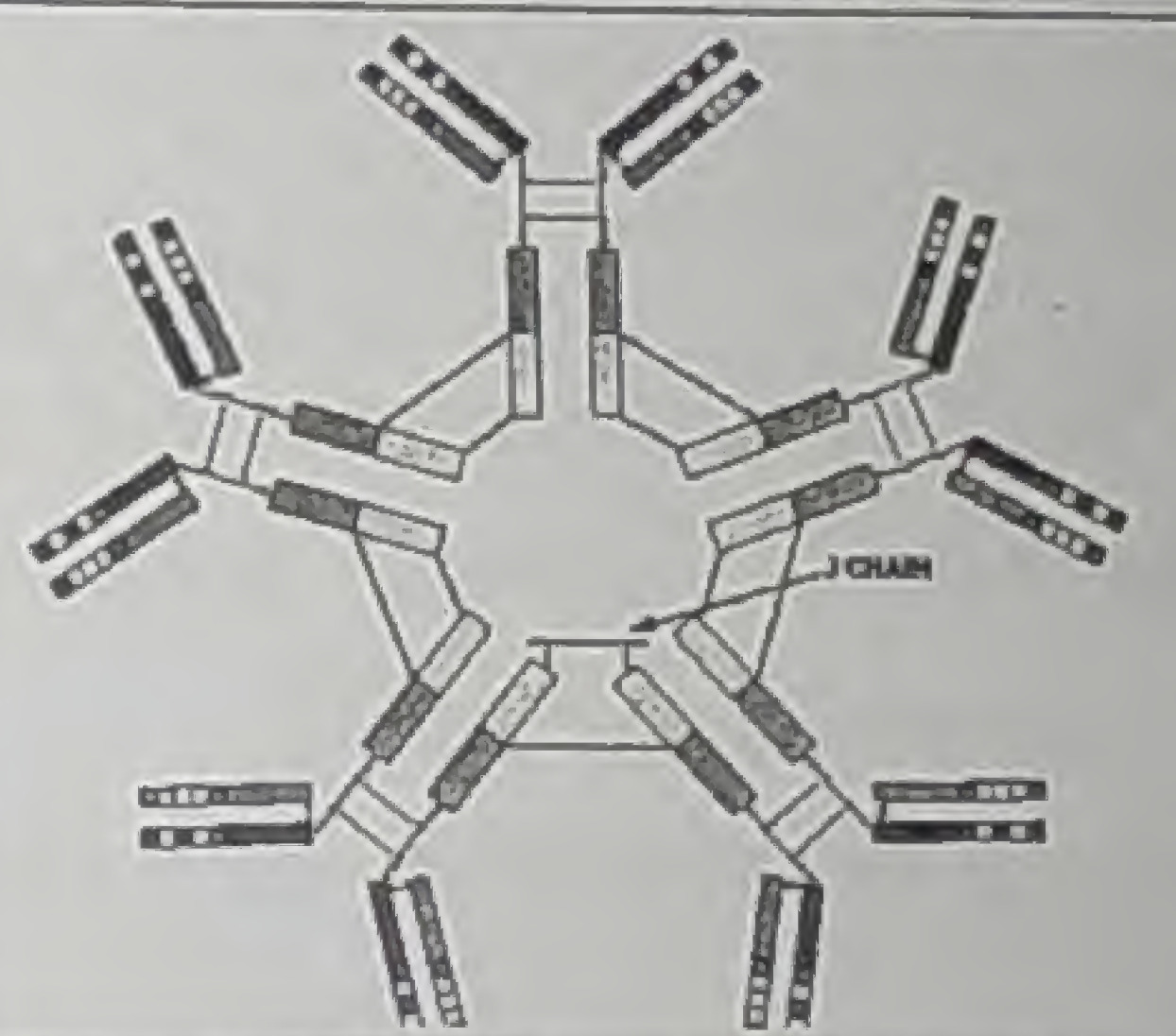
## Comparison between 1ry & 2ry humoral IR

	1ry IR	2ry IR
1-Ag	<ul style="list-style-type: none"> <li>✓ 1<sup>st</sup> exposure to Ag</li> <li>✓ High conc. is needed</li> <li>✓ T cell dependent &amp; independent Ags</li> </ul>	<ul style="list-style-type: none"> <li>❖ <i>Reexposure</i> to the same Ag</li> <li>❖ <i>Low conc.</i> is needed</li> <li>❖ T cell <i>dependent</i> Ags <i>only</i></li> </ul>
2-Responding B cell	⊕ of naïve B cells	⊕ of <i>memory</i> B cells
3- Lag period following exposure to Ag	4-7 days	1-3 days
4-Ab level	Low	High
5-Main isotype produced	IgM	IgG





# Ig isotypes

IgG	IgM	IgE
<b>I - Concentration (of total serum Igs)</b>		
80% → most abundant	5-10%	Very low
<b>II - Structure</b>		
<b>A - Heavy chain &amp; subtypes</b>		
1- $\gamma$ chain 2- 4 subtypes → 4 subclasses: i. IgG1: predominant ii. IgG2,3&4 (lowest)	1- $\mu$ chain (has an extra CH4) 2- No subtypes	1- $\epsilon$ chain 2- No subtypes
<b>B - Molecular forms &amp; MW</b>		
Monomer → <b>Lowest MW</b> 	1-Monomer (membrane bound): BCR 2-Pentamer (serum form): 5 monomer joined by i. Disulfide bonds ii. J chain : Links 2 of the Fc <b>Highest MW</b> (Highest valency: 10 Ag binding sites)	
<b>III - Distribution</b>		
Diffuse <i>easily</i> extravascular Neutralize viruses & bacterial toxins	Only Intravascular	Mucosa
<b>IV - Binding to immune cells</b>		
Binds to <b>Fc <math>\gamma</math> R</b> on phagocytes & NK cells	No	Bind to <b>Fc <math>\epsilon</math> R</b> on: i. Tissue mast cells & blood basophils ii. Blood eosinophils



IgG

IgM

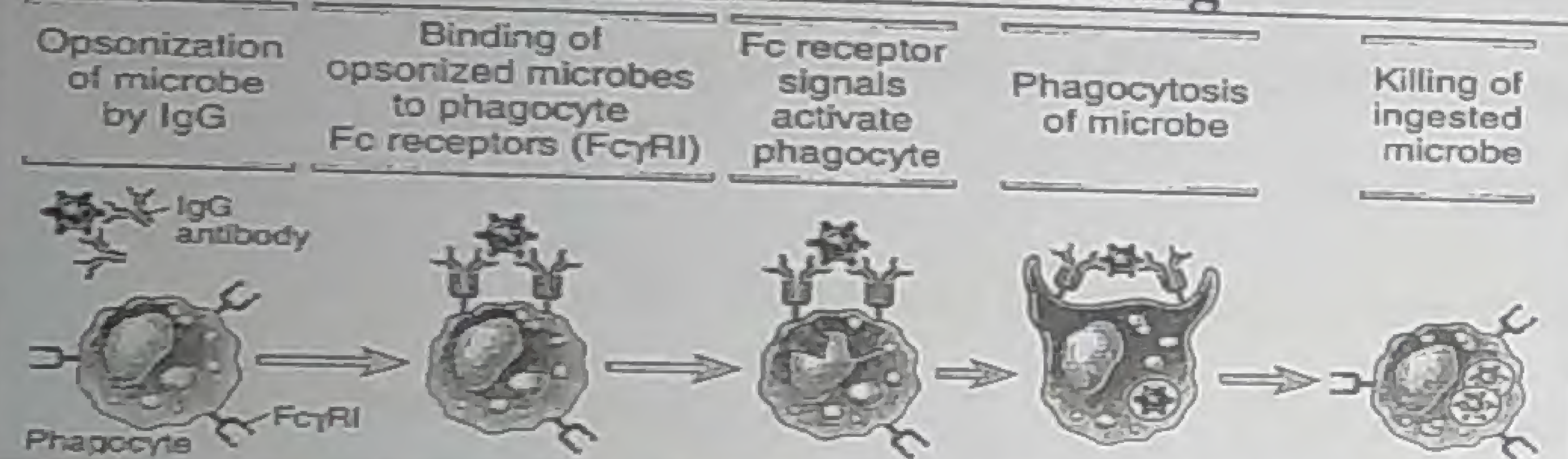
IgE

## V - Functions

## 1-Opsonization ( enhancement of phagocytosis )

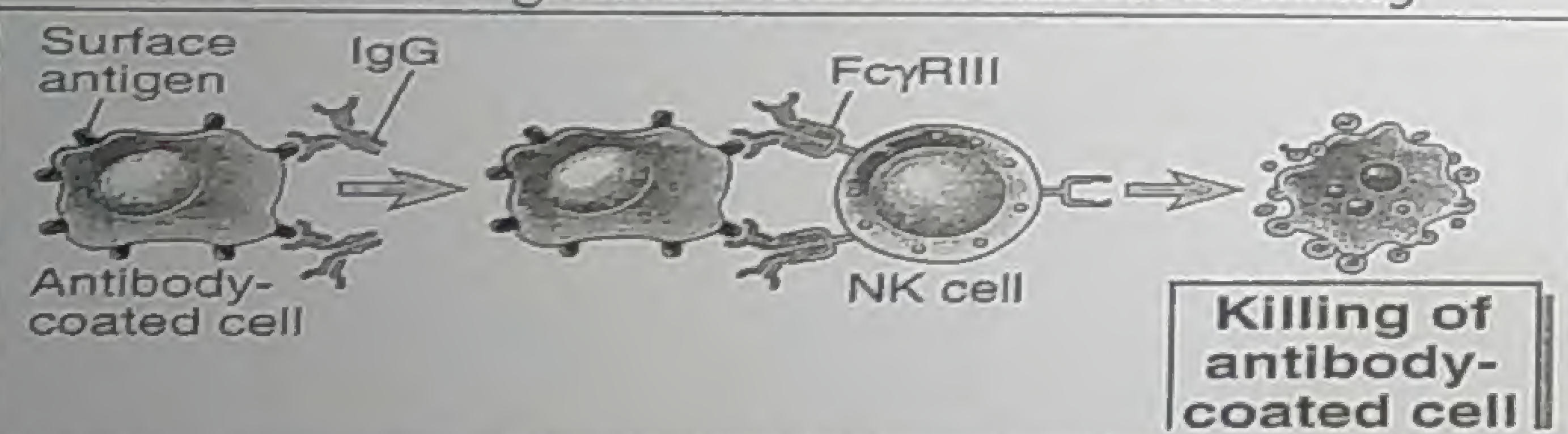
IgG1 & G3 (or C3b) coat organism  
 Bind to Fcγ R (or C3bR) on phagocytes (MQ & neutrophils)

Facilitate ingestion: IC killing



NO

## 2-ADCC ( Ab dependent cellular cytotoxicity )

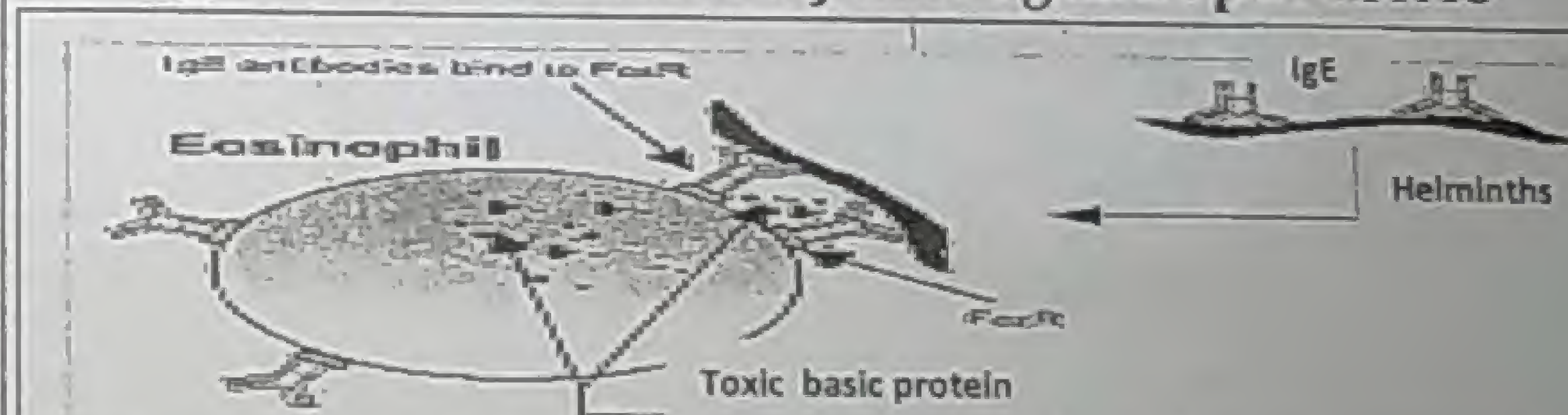
Ig G1 & G3 coat *target cells*: VIC or tumor cellBind to Fcγ R on *NK* or phagocytesRelease of granular toxic mediators: *EC* killing

NO

IgE coating helminths binds to FcεR on eosinophils

Degranulation & release of *toxic basic protein*

EC killing of worm

*IgE is the main host defense against parasites*

## 3 - Complement activation : by classical pathway

♣ G3 : Most potent

♦ G1 &amp; G2

Most efficient

NO

## 4-Neutralization

IgG binds to viruses, EC bacteria & toxins  
 Prevent their *binding* to target cell

NO



IgG	IgM	IgE	
5 - Other functions			
i . P l a c e n t a l p a s s a g e			
Only Ig (except G2) that crosses the placenta Immunity to fetus & neonate	No, but is the 1 <sup>st</sup> Ig synthesized by fetus Indicate intrauterine infection if ↑ in neonates	No	
ii . Agglutination of bacteria & viruses			
Yes	Most efficient (HMW)	ii. VD & inflammation in skin & mucosa of RT&GIT  Binds to FcεR on mast cells& basophils Degranulation on Ag binding Release of histamine& peroxidase  iii. Type I hypersensitivity(allergy) In case of excess IgE	
iii . Relation to immune response			
Most important in 2ry IR	1 <sup>st</sup> & predominant in 1ry IR		
iv - Membrane bound form			
Ag R on memory B cells	Ag R on mature B cells ( but monomeric)		

**b Degranulation and release**

Nature Reviews | Immunology

<b>Ig D</b>	
<b>Concentration</b>	<b>Functions</b>
0.2% of total serum Igs	Ag receptor (BCR) : Main membrane Bound Ig on mature B cells



## IgA

### I-Distribution & Concentration

Serum IgA

10-15%

of total serum Ig

Secretory IgA

Main Ab in *secretions*

♦ Saliva & tears ♦ Mucus of RT & GIT ♦ Breast milk

### II-Structure

#### A-Heavy chain & subtypes

α chain

2- 2 subtypes → 2 subclasses: A1 & 2

A1 is inactivated by protease of  
Neisseria, Pneumococci & H. influenza

A2 is more important in mucosal immunity

#### B-Molecular form of secretory IgA : Dimer

2 monomers joined by:

i. Disulphide bond

ii. J chain

(synthesized by submucosal  
plasma cells)

Secretory (S) component

Produced by epithelial cells

i. Facilitates IgA transport across mucosa

ii. Protects IgA from digestion by  
proteolytic enzymes in secretions

### III-Functions

Local mucosal immunity (gate keeper)

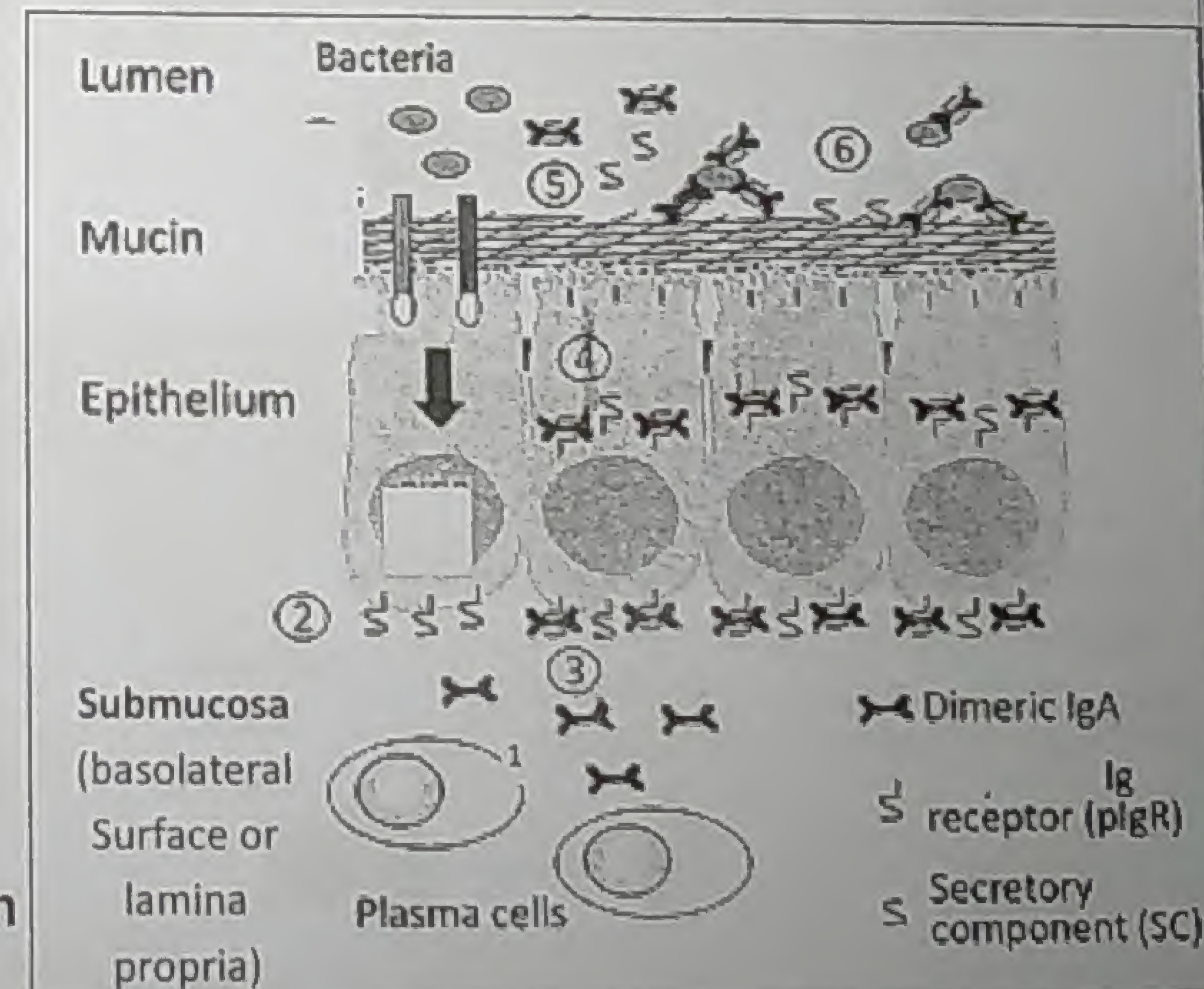
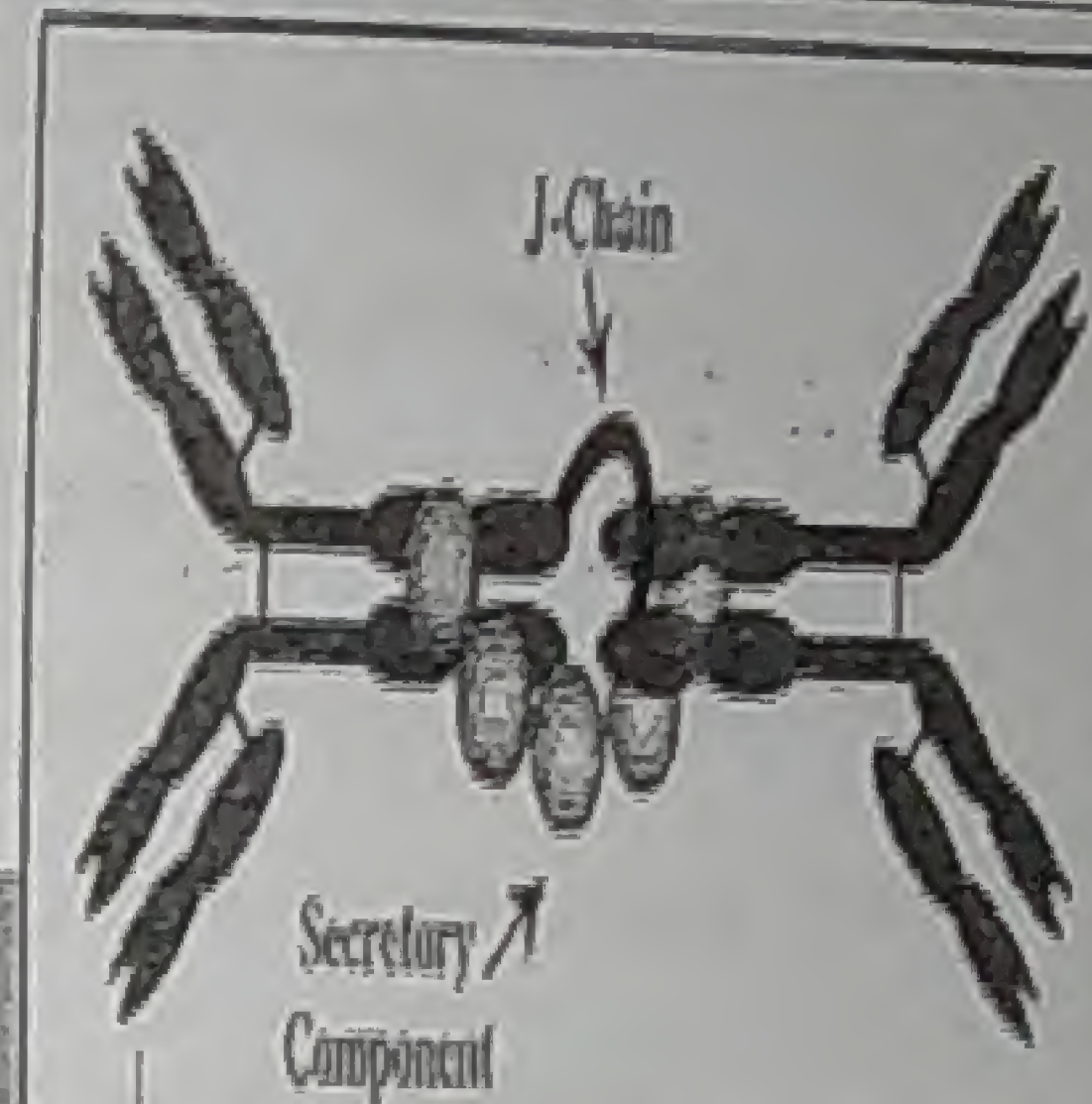
Coat bacteria & viruses in mucosa

Prevent their adherence (neutralization)

Prevent their entry into tissues

Present in colostrum & milk

Protects newborn from infection





## Ab mediated effector functions

Opsonization

IgG (M)

ADCC

IgG (M)

IgE (M)

Complement activation:

by classical pathway

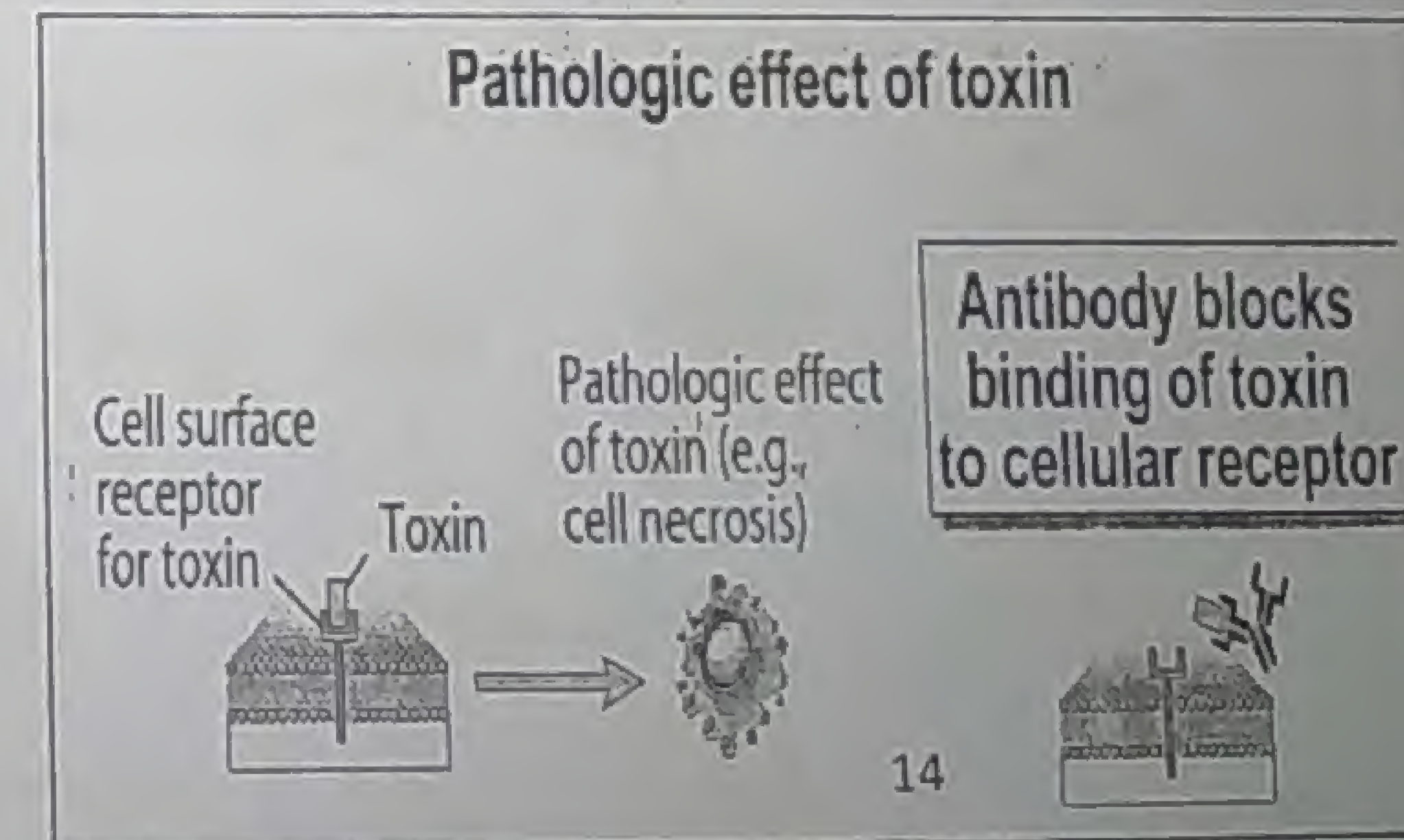
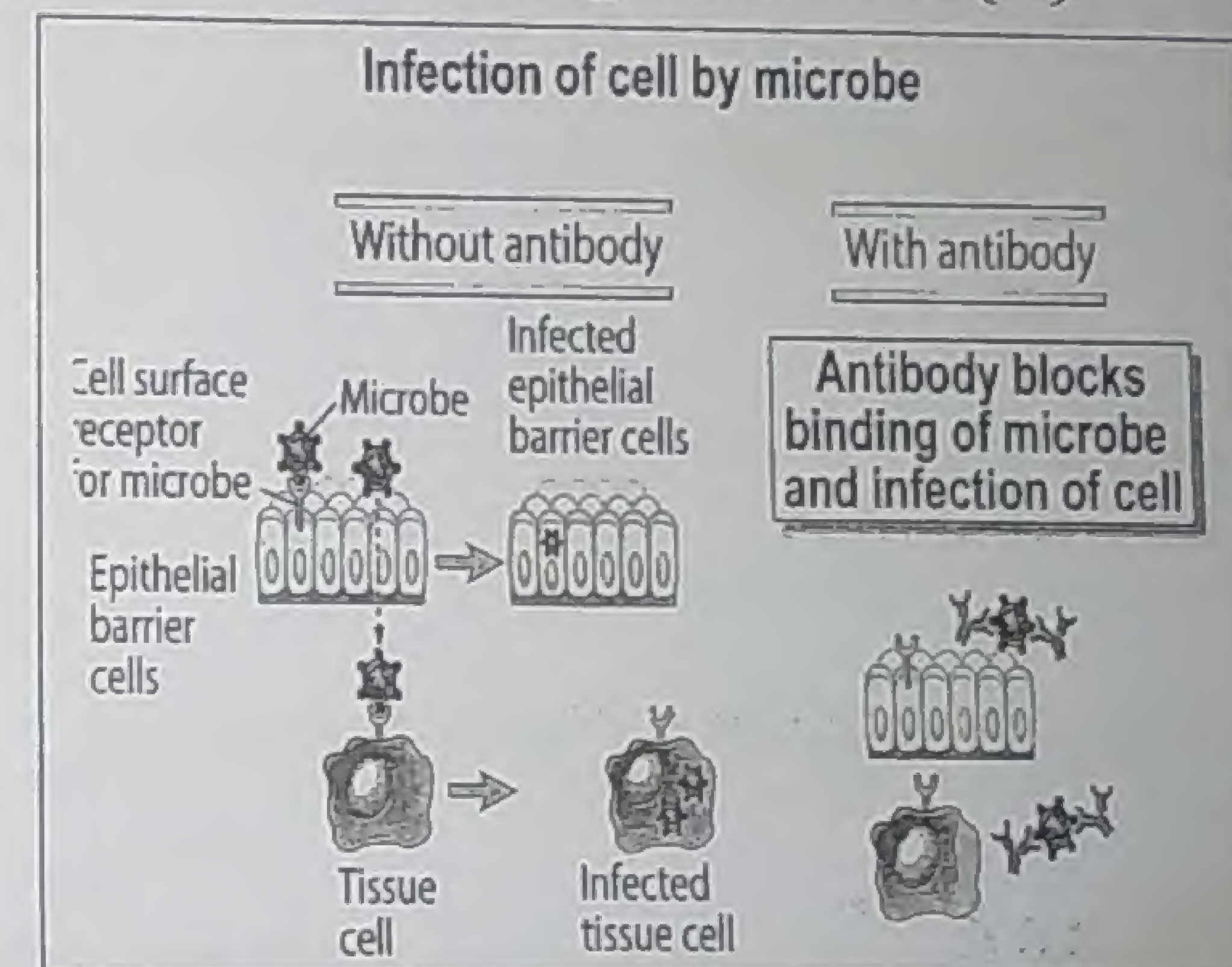
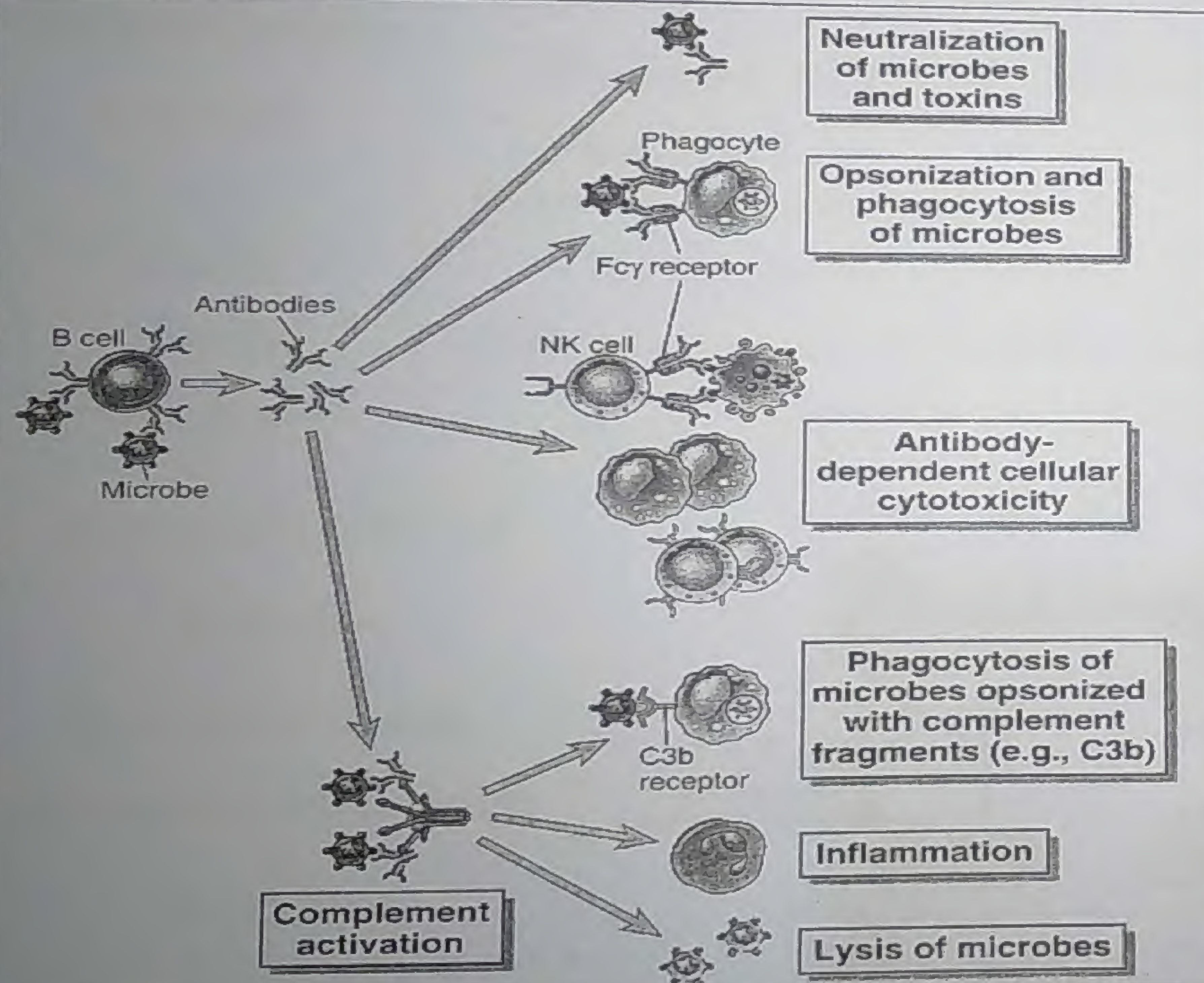
i. IgM : *most efficient*

ii. Ig G3 > G1 > G2

Neutralization of  
microbes & toxins

i. IgG: in circulation (M)

ii. IgA: in mucosa (M)





# Cytokines regulating (Adaptive immunity)

IL4	IL13	IL5
<b>Main source : Th2</b>		
	<b>IL 4</b>	<b>IL 13</b>
<b>A-Other sources</b>	Mast cells	
	NK cells	
<b>B-Biological functions</b>		
1-On B cells	i.Proliferation of B cells → differentiation into <b>plasma cells</b> → <b>Ab</b> production	
	ii.Isotype switch to IgE (Excess may induce <b>type I</b> hypersensitivity)	
2-On Th	⊕ differentiation of Th into Th2	
3- b.On MQ	⊖ MQ activation → ⊖ Th1 formation → ↓ IFN $\gamma$	
<b>C.Other functions</b>	↑ mucus production by epithelial cells	⊕ eosinophils → kill helminthes (ADCC)

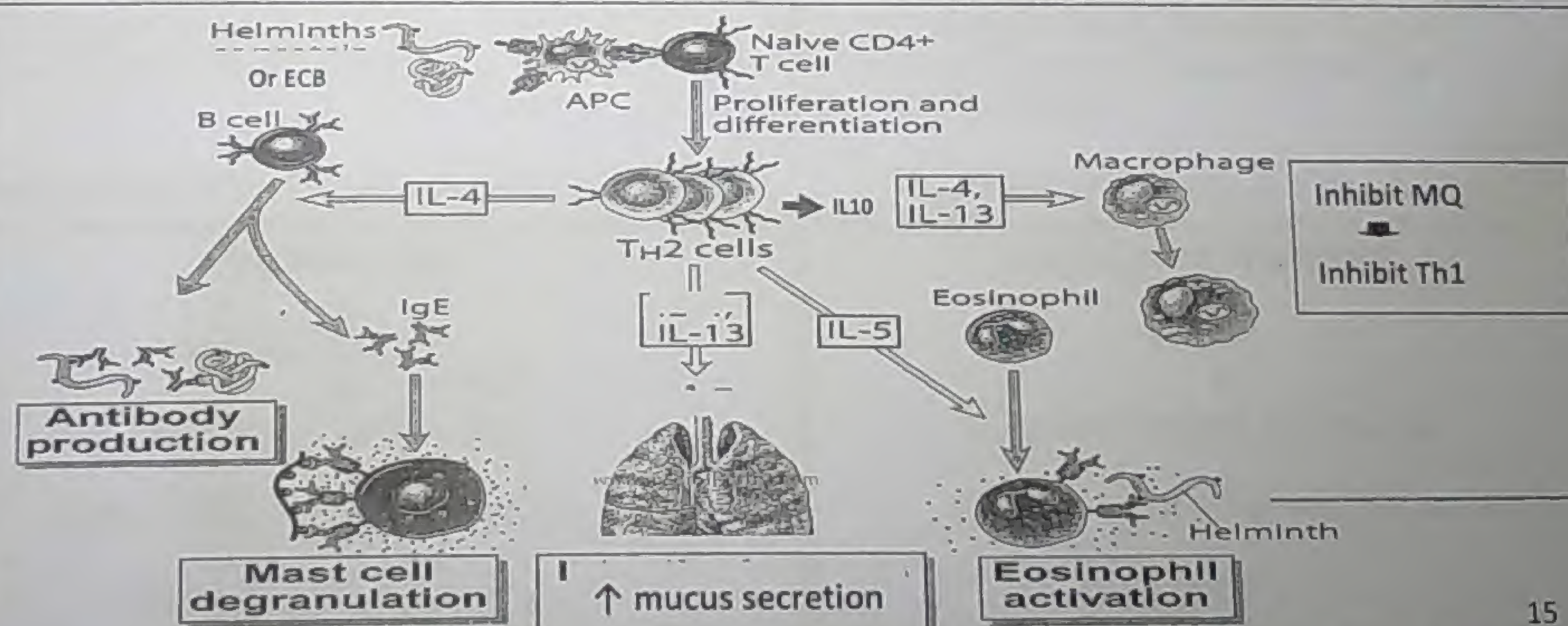
## Other cytokines from Th2

IL10 & IL6:

⊕ proliferation of B cells

differentiation into **plasma cells**

↓  
**Ab** production

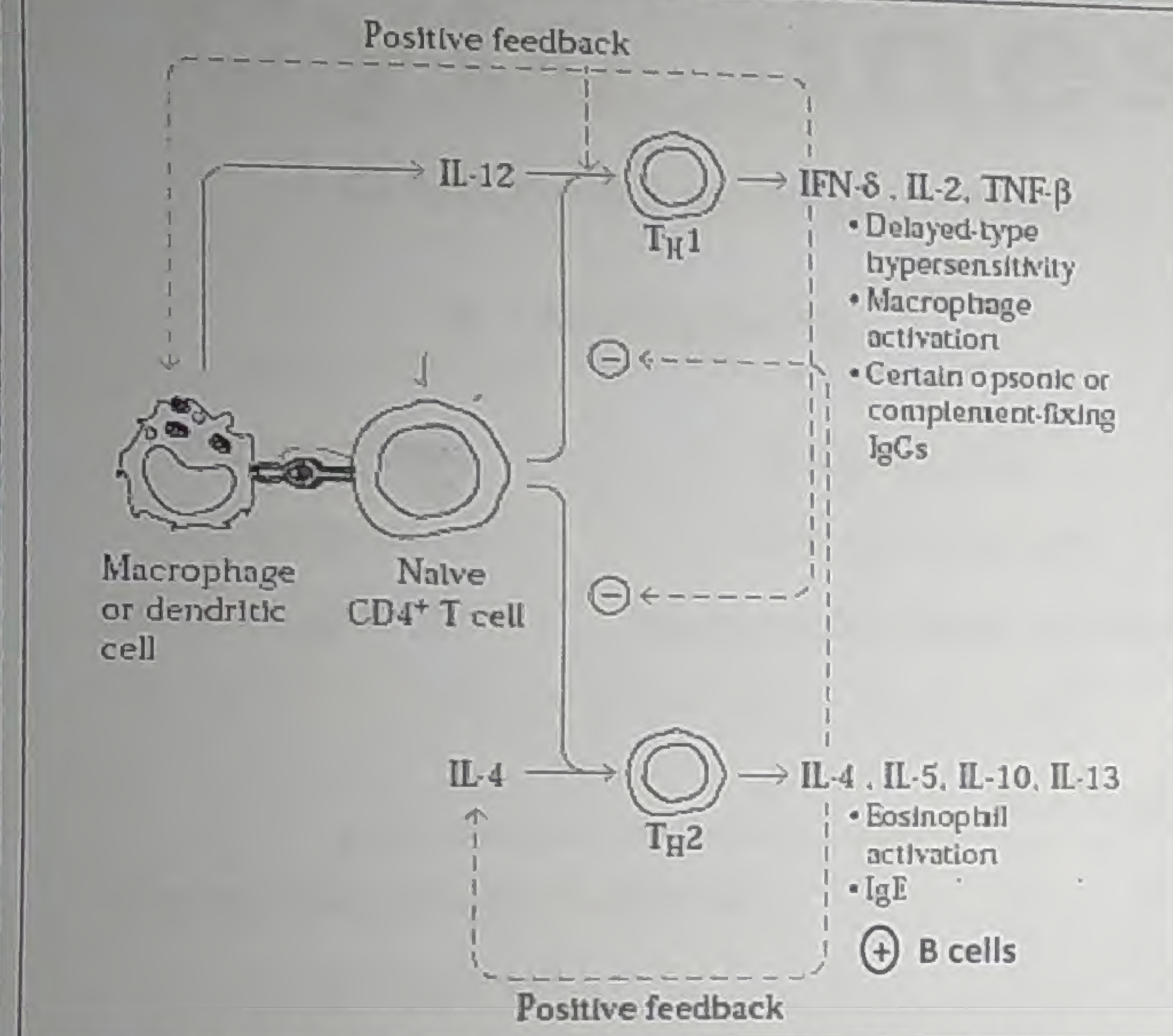




## Comparison between T helper 1 & T helper 2 cells

	Th1 cells	Th2 cells
1-Formation	By IL12 secreted from MQ & DCs	By IL4 secreted from mast cells
2-Main role	Immunity against IC bacteria, viruses, fungi & tumor cells	Immunity against EC bacteria, their toxins & parasites
3-Cytokines production	i. IL2, IFN $\gamma$ and TNF $\alpha$ & $\beta$  ii. IL3 & GM-CSFs	i. IL 4, 13, 5, 6 & 10
4-Cytokines functions	i. $\oplus$ MQ to kill IC org. (IFN $\gamma$ ) ii. $\uparrow$ cytotoxicity of Tc & NK cells (IL2) <small>(natural killer)</small> iii. $\uparrow$ production of opsonins: IgG1 & G3 (IFN $\gamma$ ) Coat org. $\downarrow$ Bind to Fc $\gamma$ R on phagocytes $\downarrow$ Opsonization	i. $\oplus$ eosinophils to kill helminthes (IL5) <small>(ADCC)</small> ii. $\oplus$ B cells $\downarrow$ $\uparrow$ Ab production & isotype switch to IgE  (IL4 & 13)
5-Harmful effects	Delayed hypersensitivity (type IV)	Anaphylaxis & atopy (type I)
6- +ve feed back & cross regulation	Cytokines produced by each subset <div style="display: flex; justify-content: space-around; align-items: center;"> <span>Positively regulate the subset producing it</span> <span><math>\longleftrightarrow</math></span> <span>Negatively regulate the other subset</span> </div>	
	IFN $\gamma$ from Th1 $\downarrow$ $\oplus$ MQ & DCs <small>(Dendritic cells)</small> $\downarrow$ More IL12 production $\downarrow$ More Th1 (+ve feedback) & $\ominus$ generation of Th2	IL4, 10 & 13 from Th2 $\downarrow$ $\ominus$ MQ $\downarrow$ $\ominus$ generation of Th1 & IL4 $\oplus$ generation of Th2 (+ve feedback)





	Humoral immunity	Cell-mediated immunity
Microbe	Extracellular microbes	Phagocytosed microbes in macrophage Intracellular microbes (e.g., viruses) replicating within infected cell
Responding lymphocytes	B lymphocyte	Helper T lymphocyte Cytotoxic T lymphocyte
Effector mechanism	Secreted antibody	Cells (T lymphocytes)
Transferred by	Serum (antibodies)	Cells (T lymphocytes)
Functions	Block infections and eliminate extracellular microbes	Activate macrophages to kill phagocytosed microbes Kill infected cells and eliminate reservoirs of infection

Each clone of B cell is **specific to 1 Ag (epitope)**

Produce only **1 type of V region (1 idiotypic)**

Present at the upper part of

Its membrane bound Ab

(Ag R)

Its 5 secreted Ab classes

(Ig M A G E D)

IgM & IgG produced from **same clone** of

B cells ( against capsule of Staph.) are :

i. Common in **variable**

ii. Different in **constant heavy**

Ig G against capsule of Staph. &

IgG against capsule of Strep.

(from **2 different B clones**) are :

i. Common in **constant**

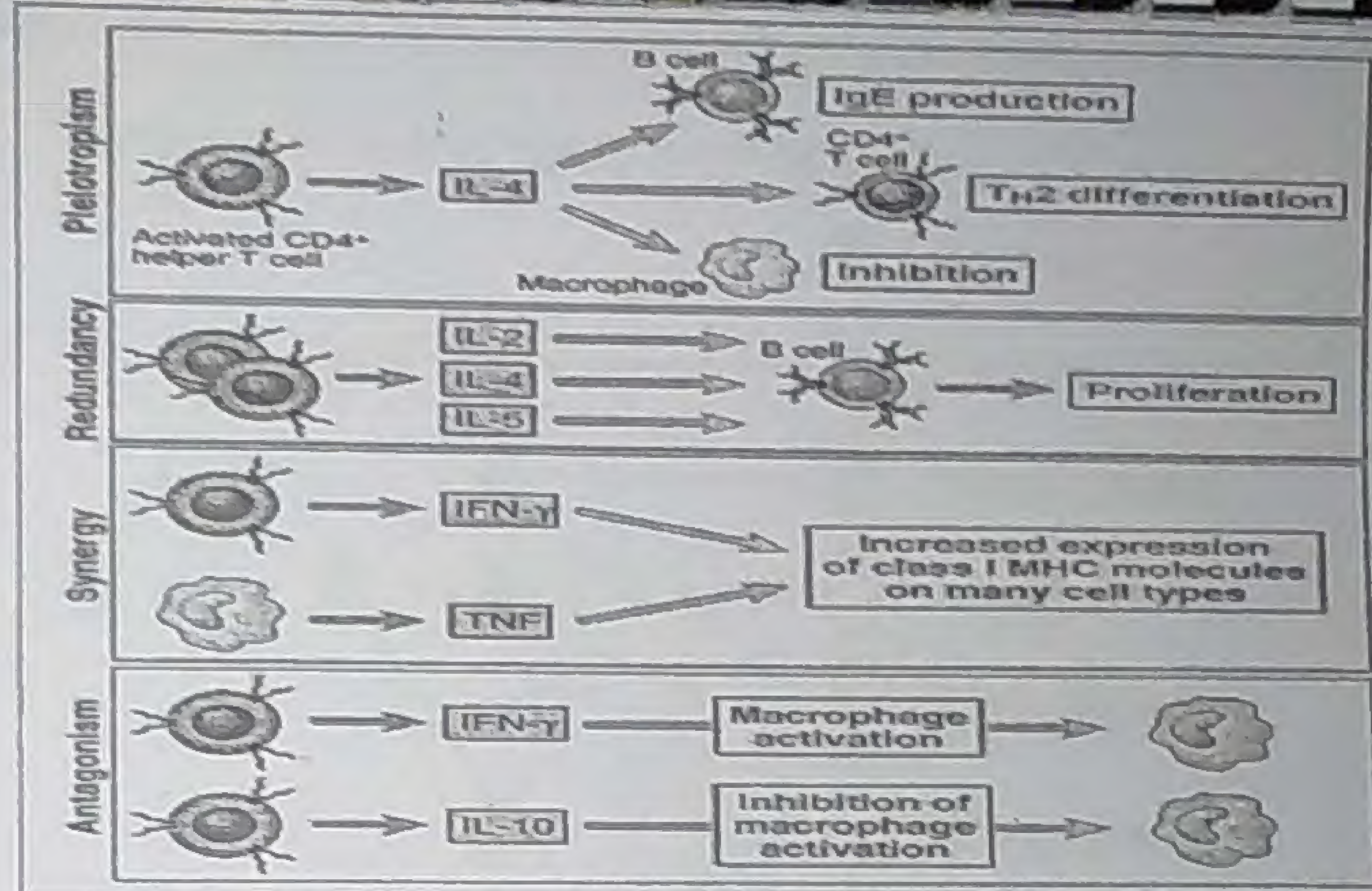
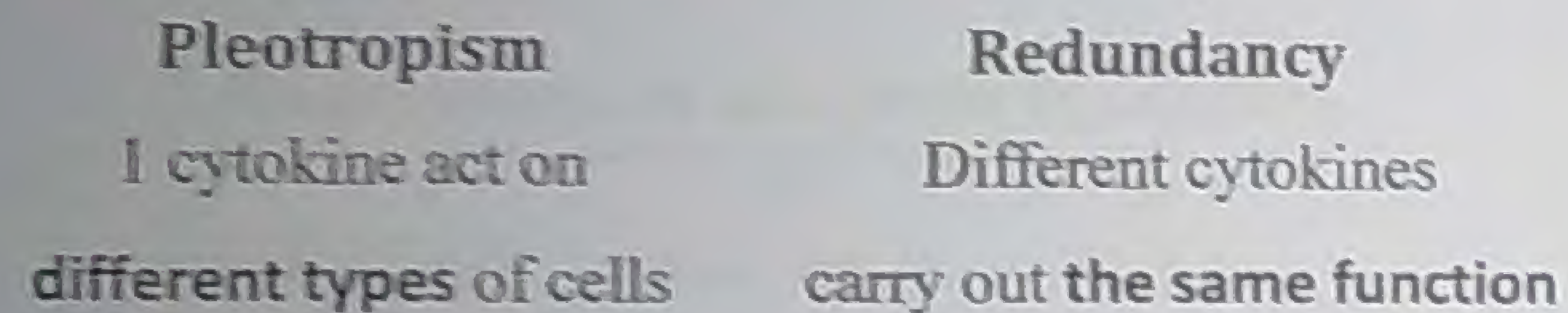
ii. Different in **variable**



# Cytokines

## General properties

### A - Multiplicity



### B - Cellular response

Expression of new functions  
in target cell

Proliferation  
of target cell

Turned down  
with inhibitory feedback mechanism

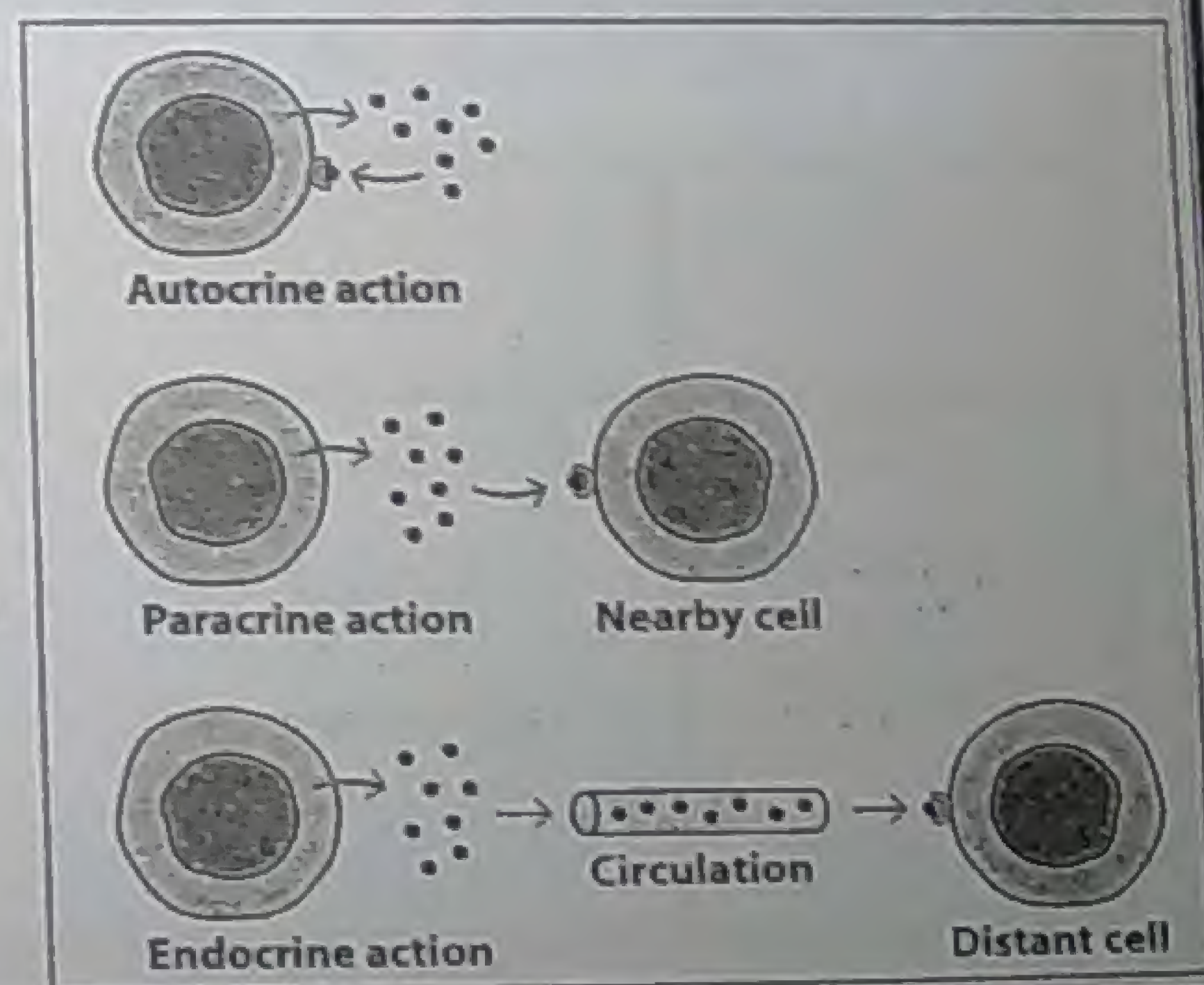
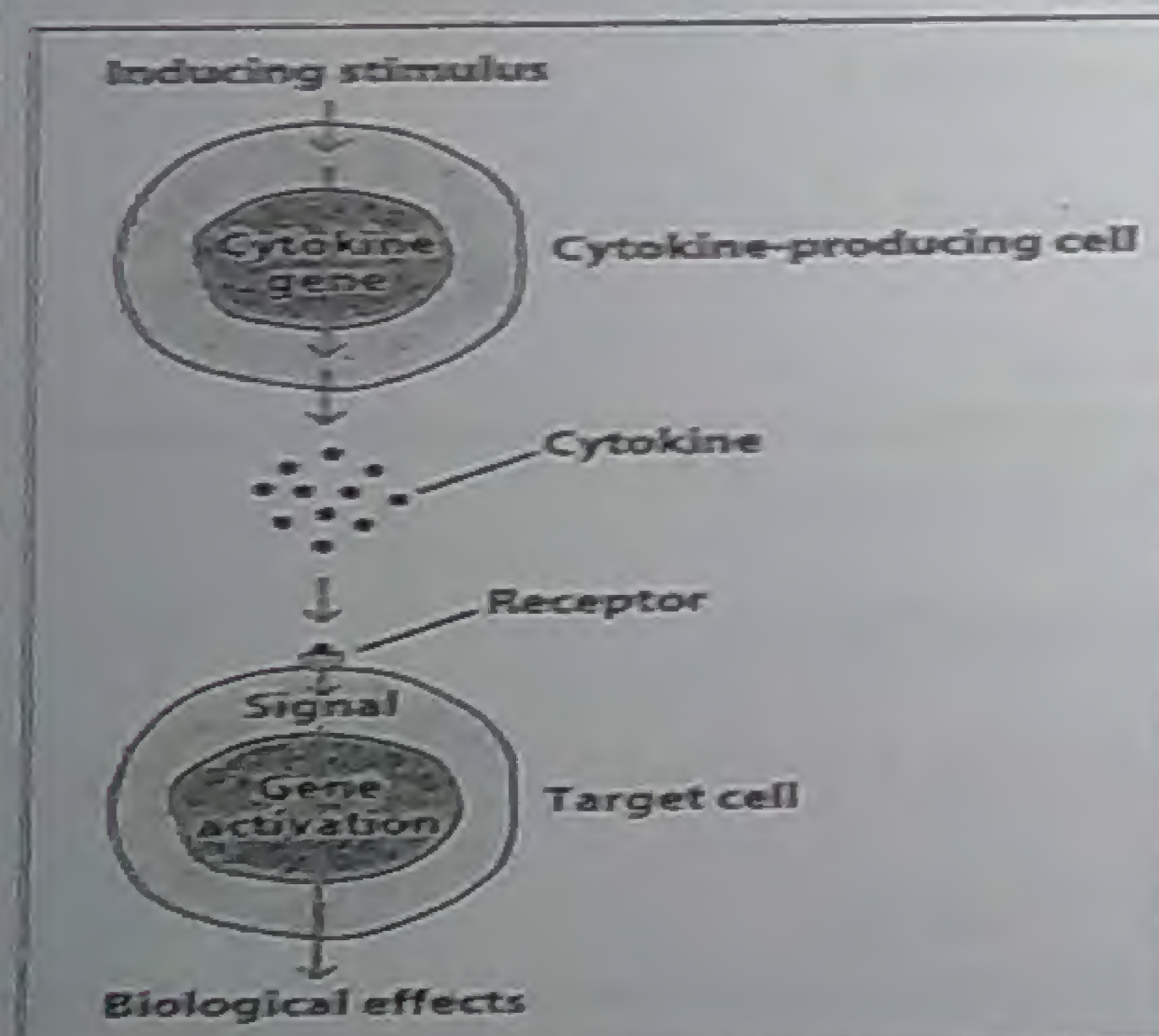
### C - Actions (Not Ag specific)

They bind to specific receptors on

Cells of origin  
↓  
**Autocrine**

Nearby cell  
↓  
**Paracrine**

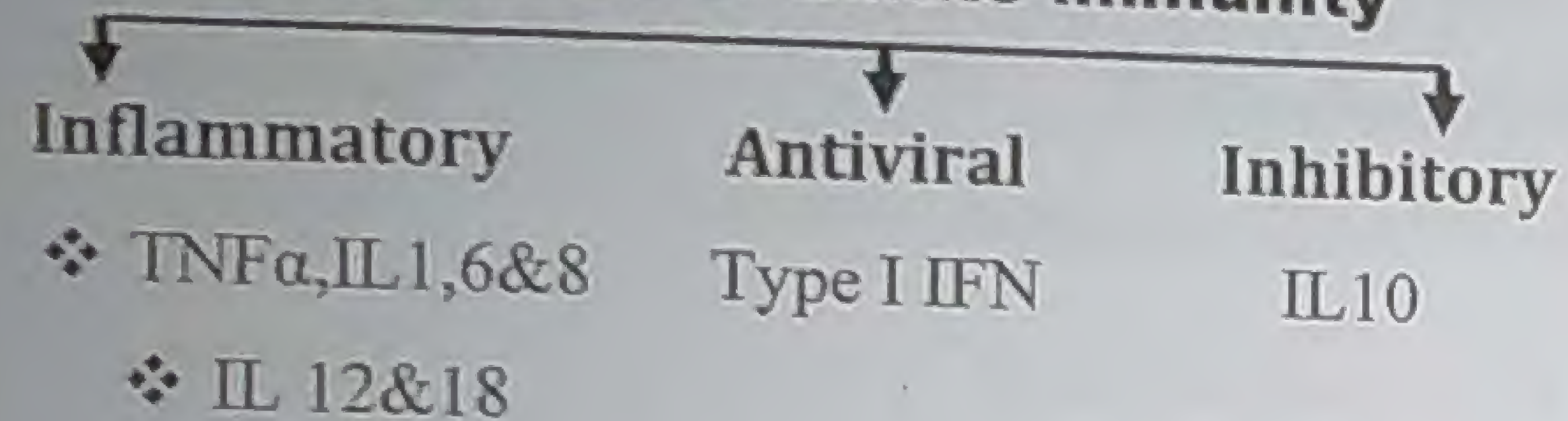
Distant cell  
↓  
**Endocrine**



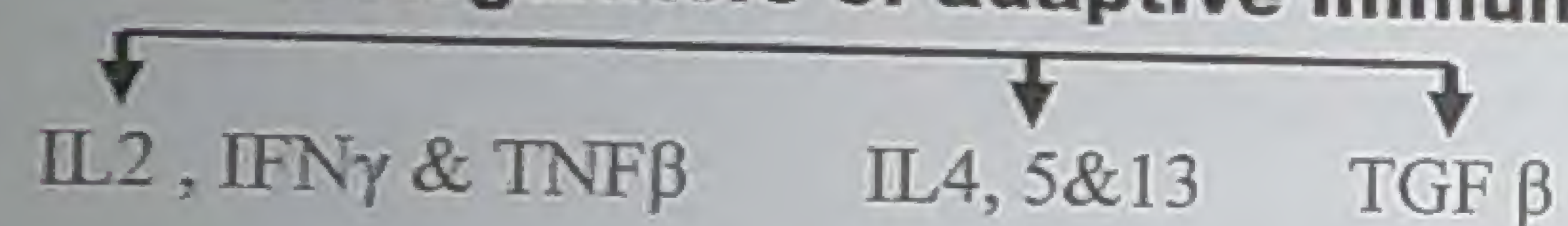


## Functions

### I-Regulators of innate immunity

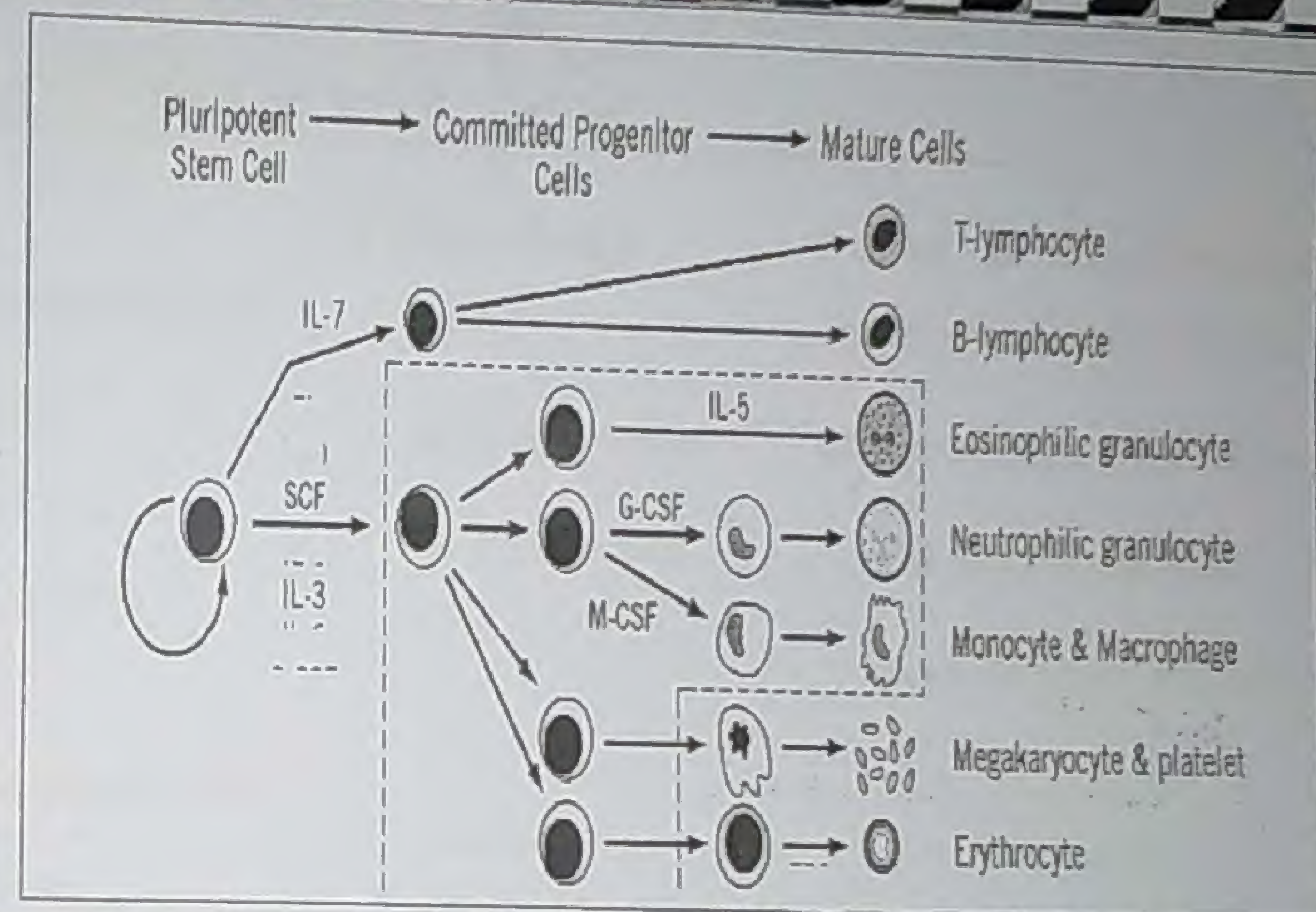


### II-Regulators of adaptive immunity



### III-Cytokines with hematopoietic effect

⊕ growth & differentiation of immature leukocytes



	1-Colony stimulating factors(CSFs)	IL3	Stem cell factor	IL7
1-Source	i. Th1 & Th2			
	ii. BM stromal cells		BM stromal cells	
	iii. Endothelial cells			
	iv. MQ			
2-Functions	⊕ production & ↑ activity of different leukocytes i. GM-CSF: ⊕ granulocytes & monocytes ii. G-CSF    iii. M-CSF	Support growth of all hematopoietic precursors	Differentiation & survival of all stem cells	⊕ immature B&T cells 18



# Granulomatous Ds

## 1-Etiology

Infection

with ICB

e.g • TB

• Leprosy

## 2-Mechanism

Chronic antigenic  $\oplus$  of MQ by surviving ICB

Sensitization of Th cells

Continuous release of cytokines

Accumulation of large n= of MQ

Release cytokines

MQ fuse to form multinucleated giant cells

## 3-Histology

▲MQ

▲Lymphocytes

▲ Fibroblasts

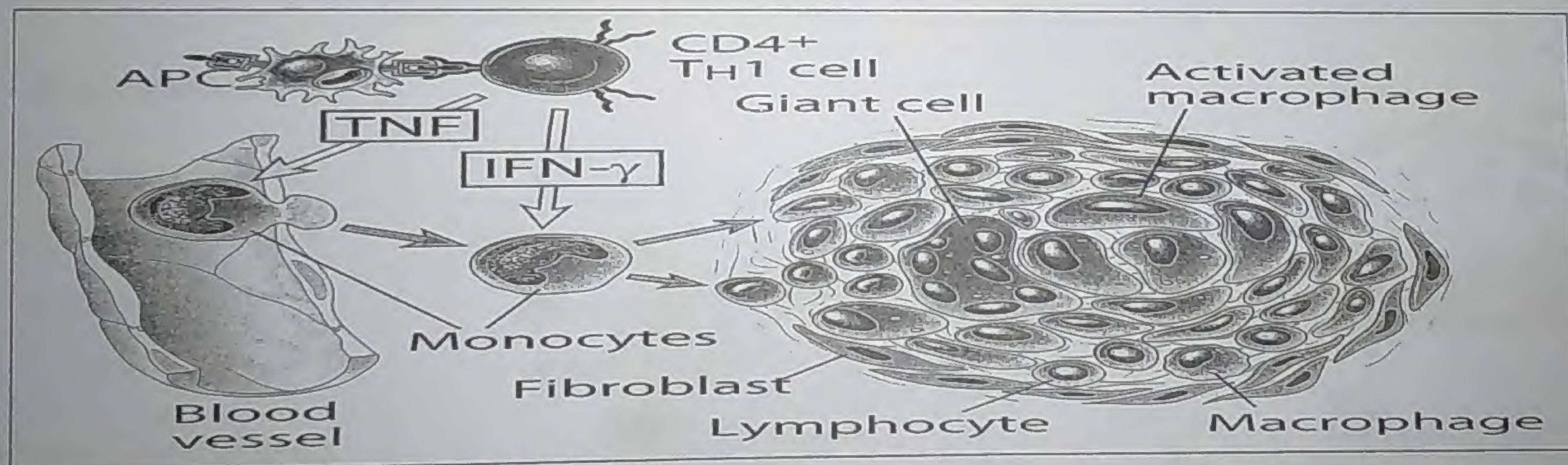
## 4-Aim & drawbacks

Attempt to wall off site

of persistent infection

but associated with

tissue necrosis & fibrosis



## Autoimmune Ds : Insulin Dependent Diabetes

CTLs react against pancreatic cells damaging it → prevent insulin secretion



# Contact Dermatitis

## 1-Etiology

Direct skin contact  
with *haptens* :

- ♣ Skin ointements.
- ♣ Hair dyes, cosmetics.
- ♣ Soap, poison ivy.
- ♣ Nickel jewelry.

## 2-Mechanism

Haptens bind to skin proteins (carriers)

**New Ags**

Ags are presented by Langerhans cells (APCs)

in skin to **CD4+Th1 cells**

Sensitization & recruitment to skin,

(together with MQ & CTLs)

CD8+ cells attack skin cells expressing MHC class I + Ag

## 3-Histology & clinical appearance

*Mononuclear infiltrate*

(peak at 12-15 hrs)

Redness, edema &

oozing eczema

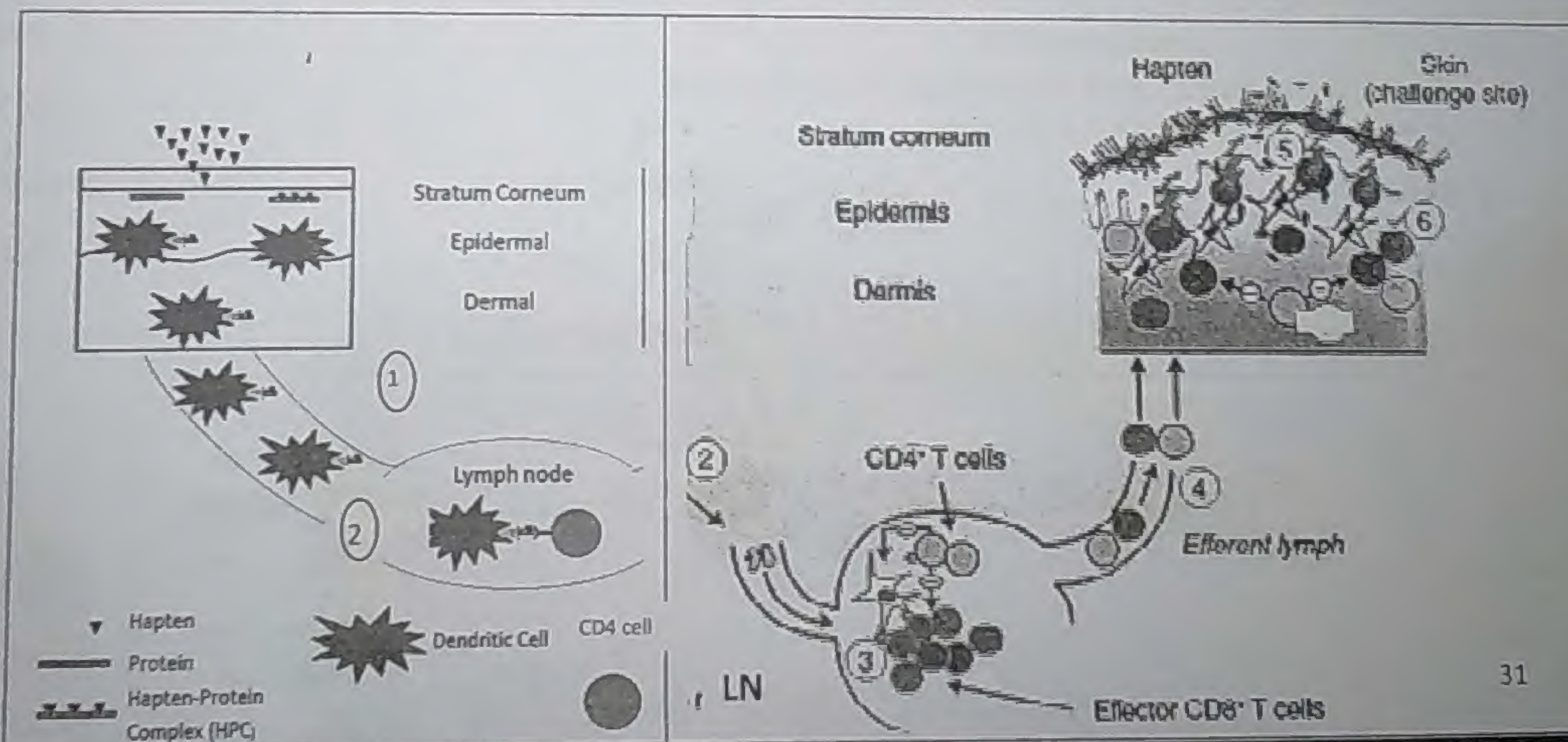
## 4-Diagnosis :

**Skin patch test**

Suspected substance is  
applied to skin for

24-48 hrs

**Inflammatory eczema**  
at the site in +ve cases





# Autoimmune diseases (AIDs)

Self tolerance	Etiology	Mechanisms of tissue damage	Laboratory diagnosis	Treatment
----------------	----------	-----------------------------	----------------------	-----------

## Definition

Adaptive IR attacking own body tissues

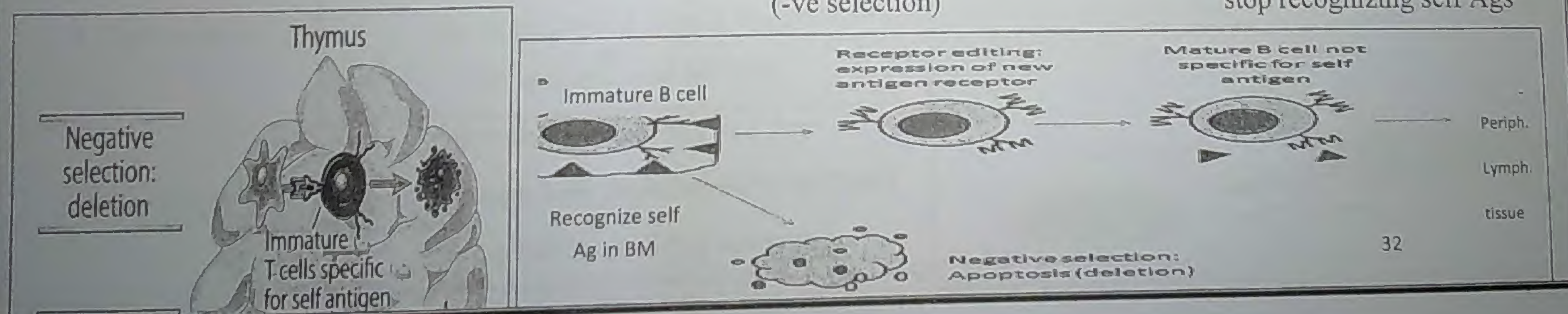
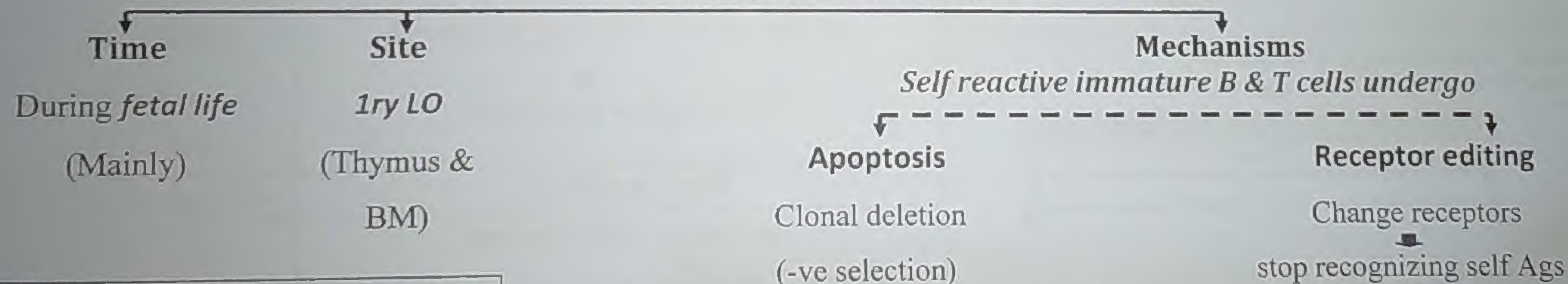
## Self tolerance

### Definition

Unresponsiveness to self Ags

### Mechanisms

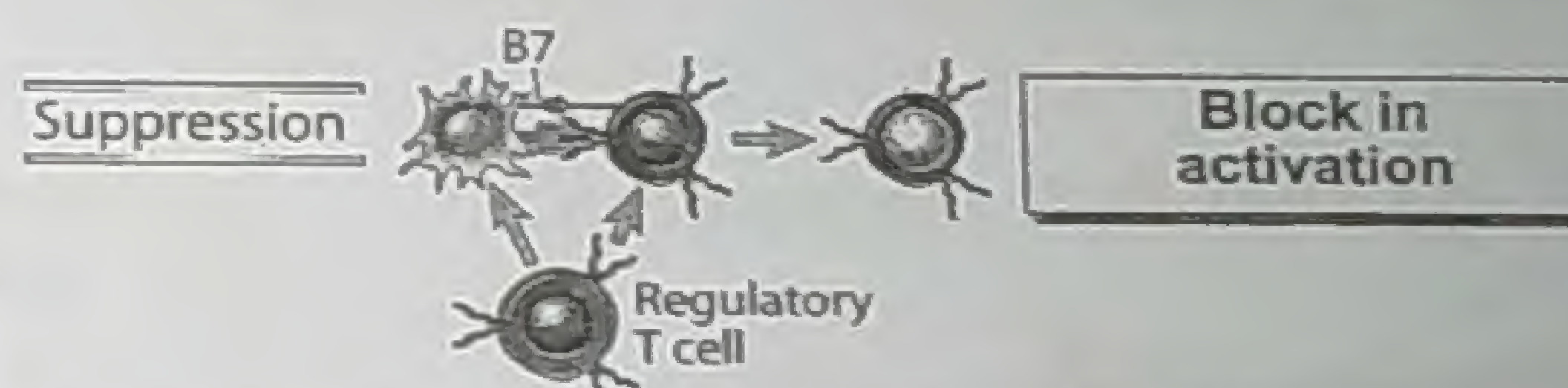
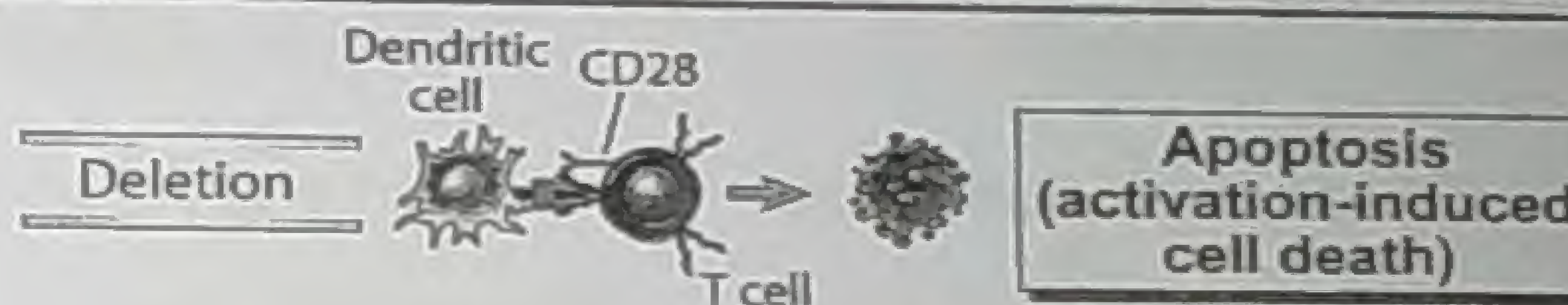
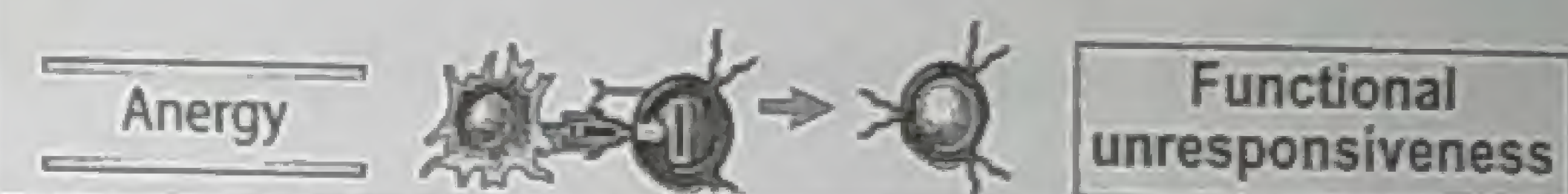
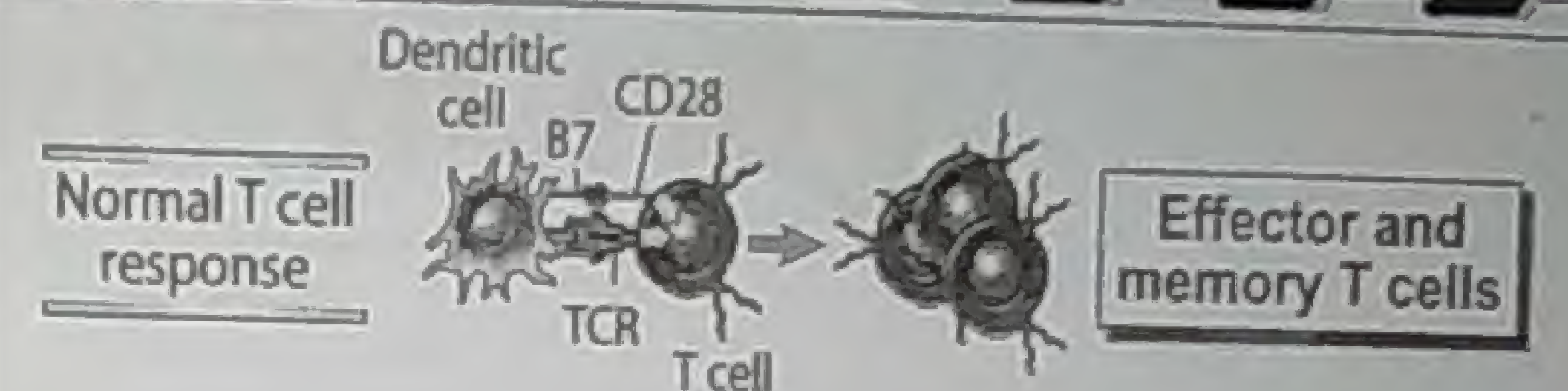
#### I- Central tolerance





## II - Peripheral tolerance

Time	Site	Mechanisms
Post natally	2ry LO (LNs & spleen)	⊖ or deletion of SR mature T cells escaping - ve selection
1-Anergy: Growth arrest		SR T cells receive antigenic signal <b>without costimulation</b> (No reaction between CD28 & CD40L on T cells with B7 & CD40 on APCs) ↓ Failure of proliferation & differentiation into effector cells
2 - Activation induced cell death		Repeated ⊕ of SR T cells by self Ags ↓ Apoptosis with deletion
3- ⊖ by T reg cells		By IL10 & TGFβ
4 - Ignorance		Sequestration of self Ags e.g Brain, cornea, lens & sperms ↓ No activation of SR cells
5-Helplessness		SR B cells recognizing self Ags don't receive help from inhibited SR T cells ↓ Unresponsive or die by apoptosis



### Antigens in Privileged Site:

Immunologically privileged sites
Brain
Eye
Testis

### B-cell responses to self or foreign





# Etiology of autoimmunity

## I - Genetic factors

Association with certain MHC genotypes

*B27 & ankylosing spondylitis*

*DR4 & rheumatoid arthritis*

♪ Diseased persons may **not** carry these alleles & these alleles may be **found in healthy** persons

Defective apoptosis

*Abnormalities in genes*

encoding proteins that **regulate lymph. apoptosis**

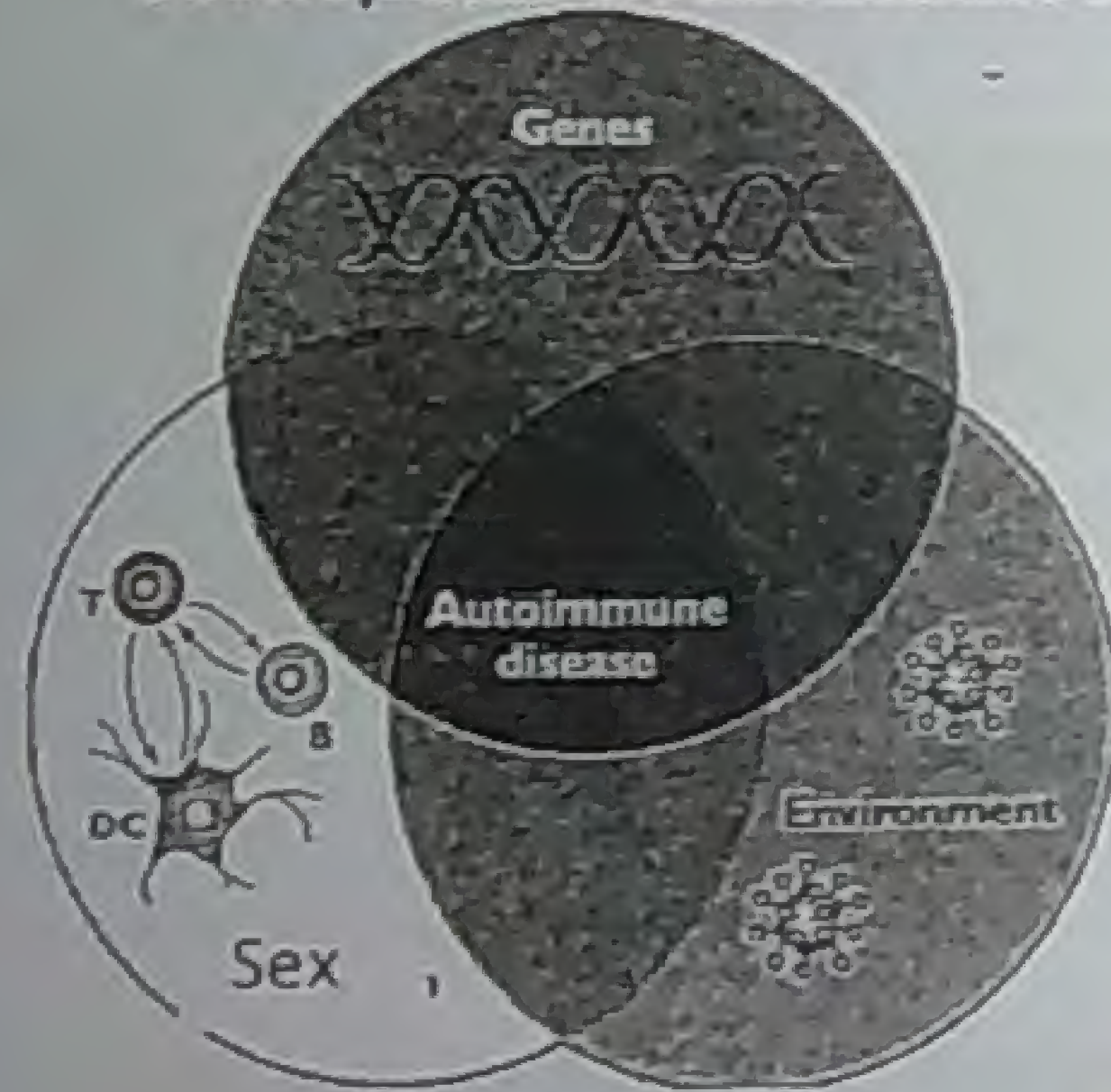
Deficiency in C1, 4 or 3

*Defective*

*complement activation*

↓ ICs clearance → SLE

Requirements for Development of Autoimmune Dis



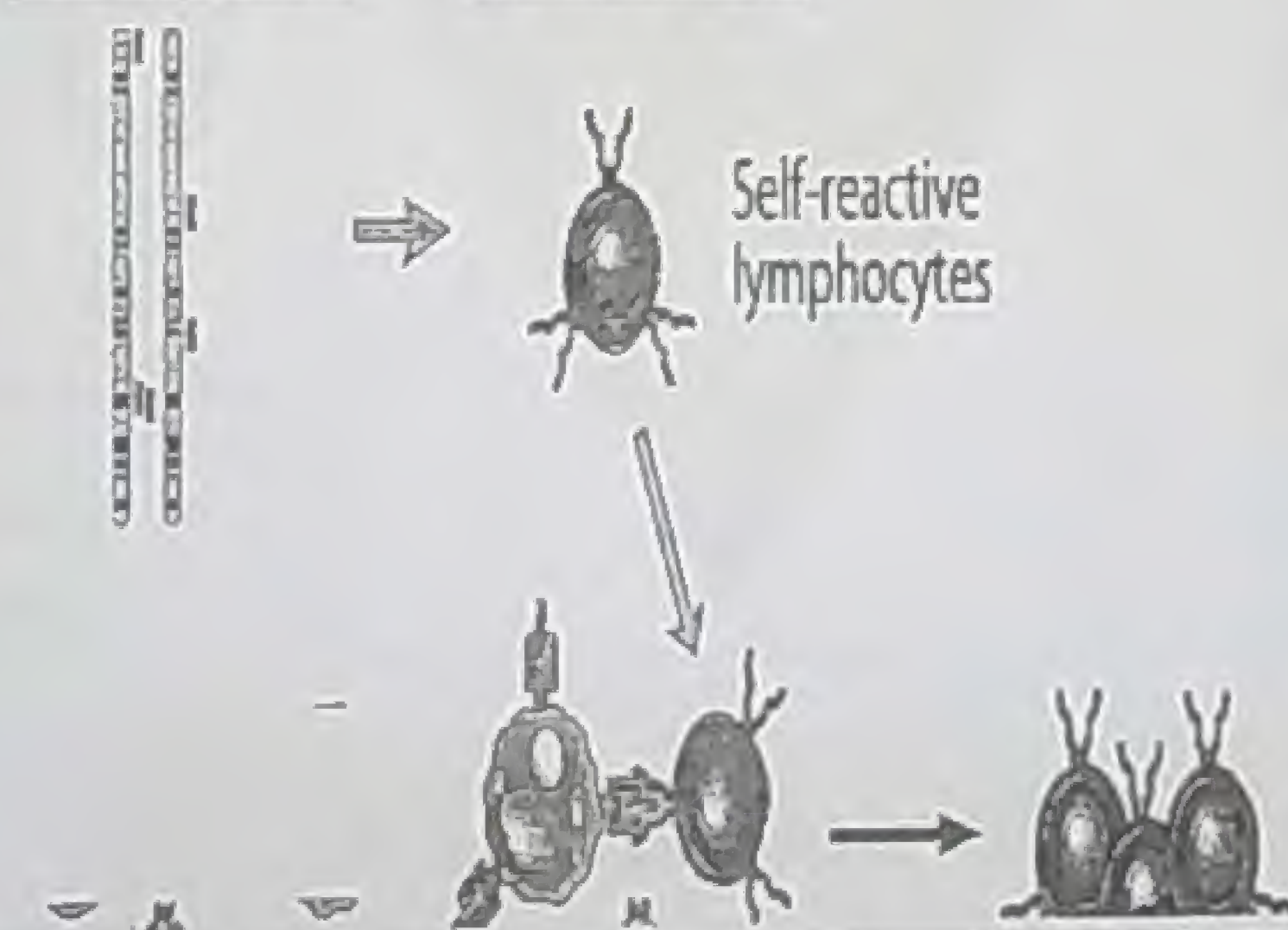
Susceptibility genes

Failure of self-tolerance

Defect in apoptosis

Genetic susceptibility

Self-reactive lymphocytes



## Complement Deficiencies

Systemic lupus erythematosus

- Deficiencies in the classical complement pathway renders pts more likely to develop immune complex diseases - SLE



## II - Sex

↑ *sex hormones* in child bearing period → ↑ AIDs in ♀

e.g Grave's ds, SLE, multiple sclerosis



### III - Environmental factors

#### 1-Infections & Trauma

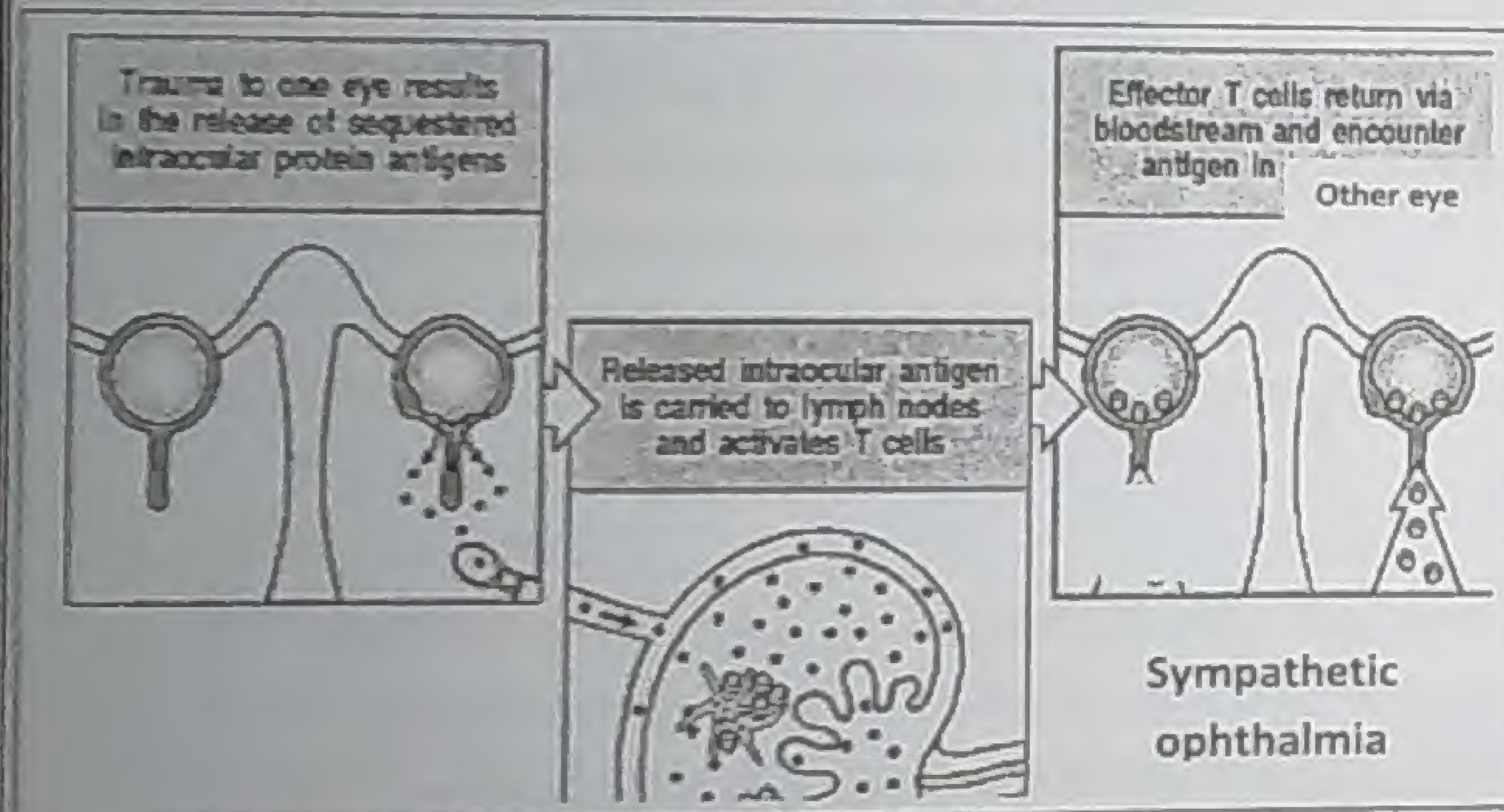
Trauma

Release of sequestered Ags

( brain,cornea,lens,sperms)

that haven't induced self tolerance

⊕ & recruitment SR T cells



Bacterial toxins

acting as superAgs

Polyclonal ⊕ of lymphocytes  
(including SR clones)

SUPER ANTIGEN

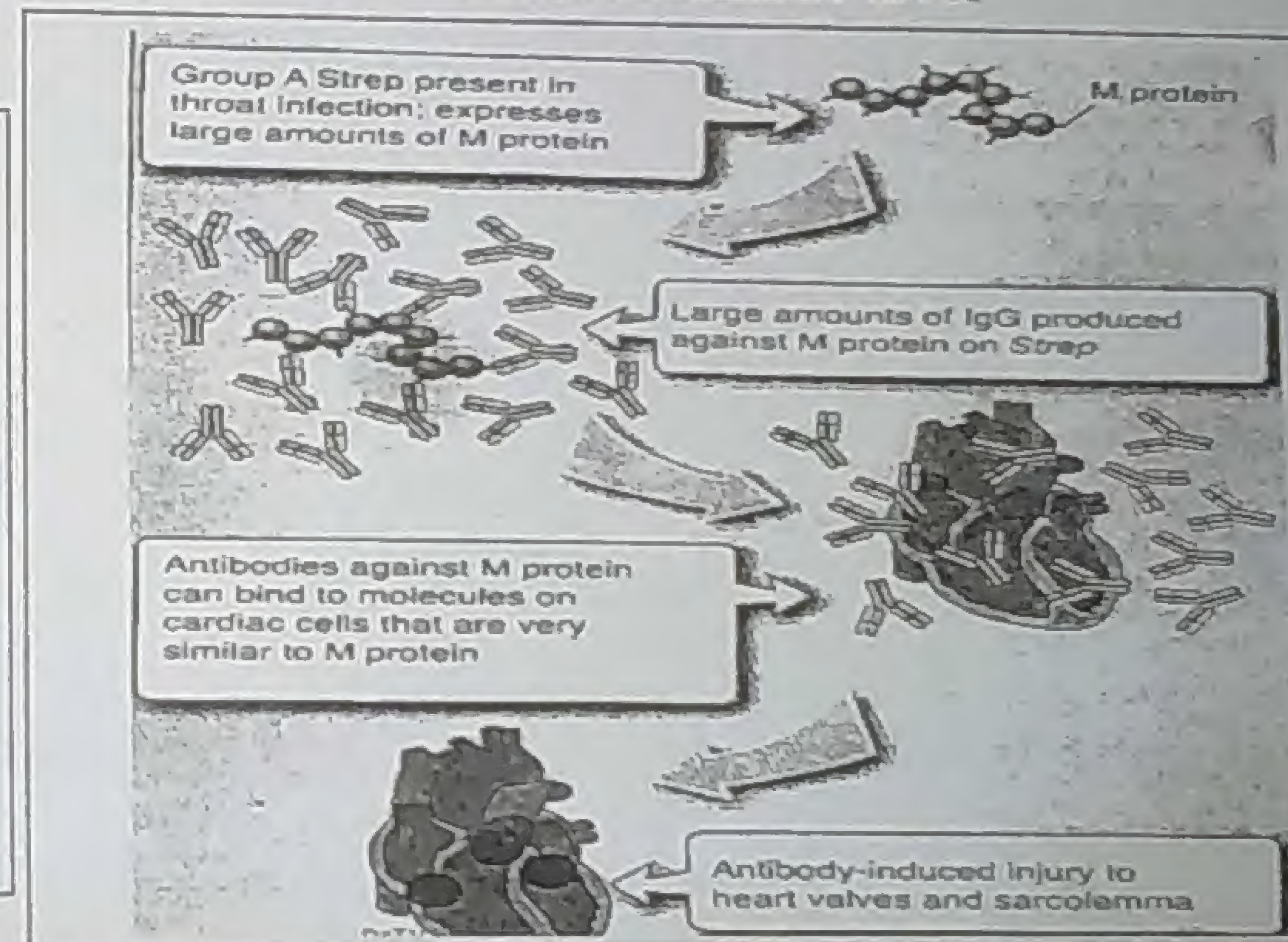


Molecular mimicry

Between Str.pyogenes Ags & heart myosin

Antistreptococcal heterophil Abs

cause rheumatic fever



#### 2 - Loss of suppression

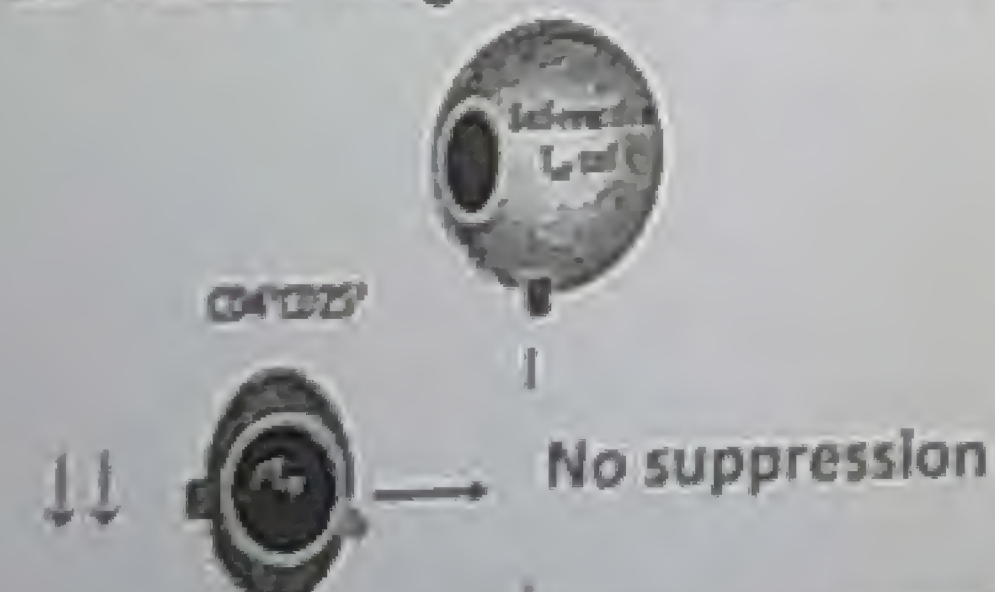
↓ n of T reg with age

Suppressed SR cells

become active

↑ AIDs in elderly

Functional deficiency in  
CD4<sup>+</sup>CD25<sup>+</sup> Treg cells in autoimmunity



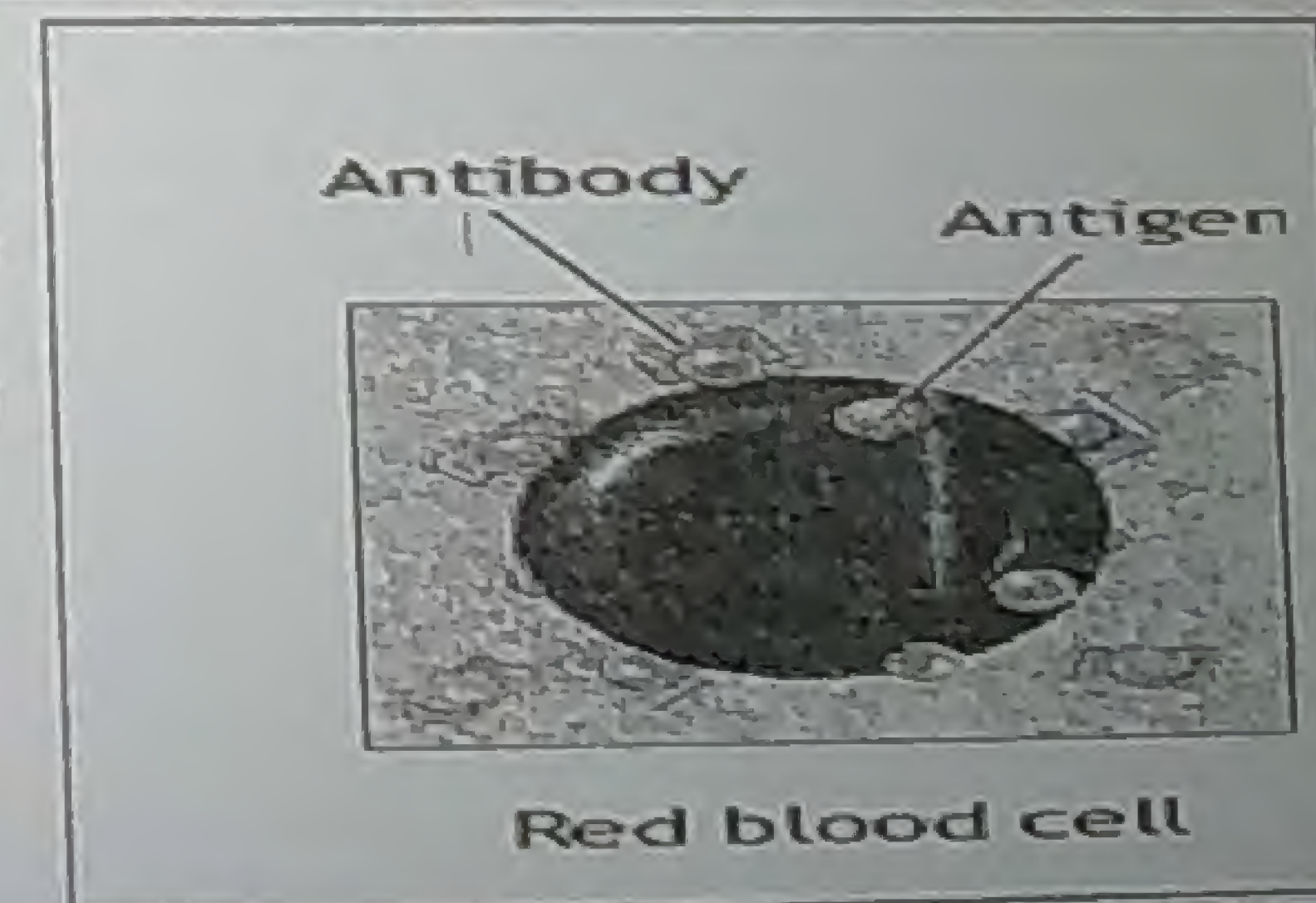
#### 3-Alteration of self Ags by :

drugs, chemicals or viral inf.

Drugs (haptens) coupling with RBCs

alter self Ags

AI hemolytic anemia 5





## Essay questions

### 1- Compare & contrast :

- a. +ve & -ve selection of Tcells.
- b. MHC class I&II.
- c. Killing mechanisms of MQ &CTLs.
- d. Tc & NK cells
- e. Naïve &memory T cells.

### 2- Give a short account on :

- a. Importance of MHC mol. In health & disease.
- b. Functions of APCs.
- c. IL12.
- d. Down regulation of cell mediated IR.
- e. Mechanisms of evasion of ICB or viruses or fungi from IR.
- f. Septic shock induced by superAgs
- g. Tuberculin test or contact dermatitis.
- h. Anergy and ignorance as mechanisms of peripheral tolerance.
- i. T cell anergy.

### 3- Give reasons :

- a. Negative selection is an important step that occurs during maturation of lymphocytes.
- b. IC Ags are presented in different way in comparison to EC Ags.
- c. B7 molecule plays a dual role in immunity.
- d. Type I interferon is the most potent antiviral cytokine.
- e. Central tolerance to self Ags.
- f. Infection & trauma may be associated with autoimmune ds.

### 4- Define superAg , give mechanism of action & examples.



**Immunology 4**

**Immunization**



# Immunization

## Definition

Induction of protection against infection with pathogenic organisms by artificial safe procedure

## Ways

	Active immunization : Vaccination	Passive immunization
1-Method	Using <b>killed or attenuated</b> microbe or <b>part of it</b> ⊙ host to produce Abs/ or immune-reactive cells	Using <i>preformed components of IR</i> : Abs or CTLs
2-Onset of protection	<b>Delayed</b> : appears after a lag period	<b>Immediate</b>
3-Duration of protection	<b>Long term</b> due to memory cell	<b>Short term</b>

## Comparison between active & passive immunity

	Active immunity	Passive immunity
I-Acquisition		
A-Natural	<p style="text-align: center;">Infection</p> <p style="text-align: center;">↓      - - - - -      ↓</p> <p style="text-align: center;">Clinical                  subclinical</p>	<p style="text-align: center;">Transfer of maternal Abs</p> <p style="text-align: center;">↓      - - - - -      ↓</p> <p style="text-align: center;">Transplacental: IgG      In colostrum &amp; milk : sIgA</p>
B-Artificial (immunization)	Vaccination	Injection of preformed Abs or CTLs
II-Onset & duration of protection	.....	.....
III-Type of protection	<p style="text-align: center;">i. Protective immunity</p> <p style="text-align: center;">ii. Immunological memory</p>	<p style="text-align: center;">i. Transient protection</p> <p style="text-align: center;">ii. Alleviation of preexisting ds</p>



# Active immunization by vaccines

## Definition of vaccines

Any preparation producing *immunity to a ds*

By (+) the production of Abs or cellular immunity

Without causing severe infections

## Strategies for developement of vaccines

### I-Whole organisms vaccines

	<b>Killed ( inactivated ) vaccines</b>	<b>Live attenuated vaccines</b>
<b>1-Idea</b>	<p>Org.is killed ( inactivated)</p> <div> <div>No replication ↓ No disease</div> <div>Maintaining epitopes on Ag</div> </div>	<p>Org.is attenuated</p> <p>Transient replication in host cell</p> <p>Mimics natural infection but in <i>mild</i> form</p> <p>No disease</p>
<b>2-Method</b>	<p>1-Heat</p> <p>2-Chemicals: formaldehyde or alkylating agents</p>	<p>1-Repeated subcultures under abnormal conditions</p> <p>2-Genetic engineering</p>
<b>3-Administration</b>	Injection	<p>Natural routes of infection:</p> <p>Oral or intranasal</p>
<b>4-Examples</b>	Salk vaccine of polio	Sabin vaccine of polio



<b>Killed Vaccines</b>		<b>Live attenuated vaccines</b>	
<b>5-Disadvantages</b>		<b>5-Advantages</b>	
i. Given by injection		i. Given orally or intranasal	
ii. Inefficient IR		ii. Efficient IR	
a- Humoral		Induce both systemic(IgG) & local (sIgA) immunity	
Induce systemic (IgG), but not local (sIgA) immunity		b- Cell mediated	
Weak		Strong	
c-Duration		Long lasting	
Short		Multiplication of atten.org.in body → similar to natural ds	
No multiplication in body → not similar to natural ds		iii. Herd immunity : Unimmunized individuals are indirectly protected by surrounding immunized individuals	
No		Yes	
		Live atten.strains are transmitted to other community members by fecooral route	
iv. Failure to kill the org. → ds			
<b>6-Advantages</b>		<b>6-Disadvantages</b>	
a. Stable : don't need cold storage		a. Low stability: need cold storage	
b. Safe : no contraindications		b. Safety problems of attenuated strains	
		i. Serious illness in IS pts or during pregnancy (fetal damage)	
		ii. Insufficient attenuation	
		Induce same complications as those seen in natural ds	
		e.g Measles vaccine causes <b>encephalitis</b> in small % of recipients	
		iii. Reversion to virulence → ds	



## II-Vaccines containing a portion of organism e.g capsule

### Advantages

Avoid toxicity &  
risk of infection  
due to retained virulence

### Disadvantages

Polysaccharide capsules are  
thymus independent Ags  
↓  
*Conjugated to carrier protein*  
to become more immunogenic

### Examples

Capsule & conjugated vaccine of:  
i. Strept. pneumoniae  
ii. Meningococci

## III-Synthetic polypeptide vaccine

### Preparation

*Synthetic polypeptide similar in its a.a sequence  
to viral or bacterial Ag*

↓  
Used as vaccine

### Disadvantage

Weak immunogen

## IV-Inactivated toxins : toxoid

### Preparation

Bacterial toxins are *inactivated (modified)* by formaldehyde

↓  
*Toxoid : Non toxic, but immunogenic*

↓  
Induce antitoxins that neutralize toxins

### Uses

To prevent infection caused by  
exotoxin producing bacteria  
e.g C. diphtheria & Clostridia tetani



## IV-Anti-idiotypic Ab vaccine

### Preparation

Idiotypic (a.a. sequence in Ag binding site of Ab)  
is injected into animal

Production of **anti-idiotypic**

(Abs to idiotype)

that *mimics* part of

the 3 dimensional structure

of its specific Ag

Used instead of it as vaccine

Induce an IR against infectious ds

e.g herpes, hepatitis B, polio & rabies

### Value

When the original Ag  
isn't suitable

e.g

i. Polysaccharide

ii. Lipid A bacterial toxin

### Advantage

Induce memory

which polysaccharide

& lipid don't induce

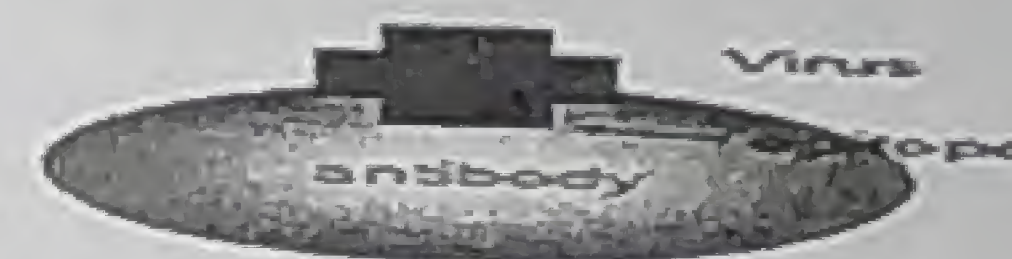
unless conjugated

with protein

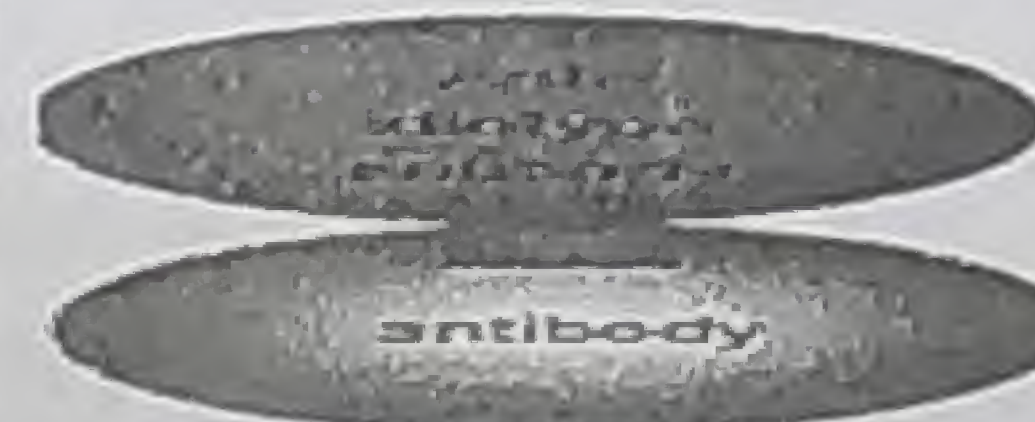
## Anti-Idiotypic Vaccines

1.

Antibody with epitope  
binding site



2.



Make antibody against  
antibody idiotype

Anti-idiotypic antibody  
mimics the epitope



3.

Use anti-idiotypic antibody as injectable  
vaccine



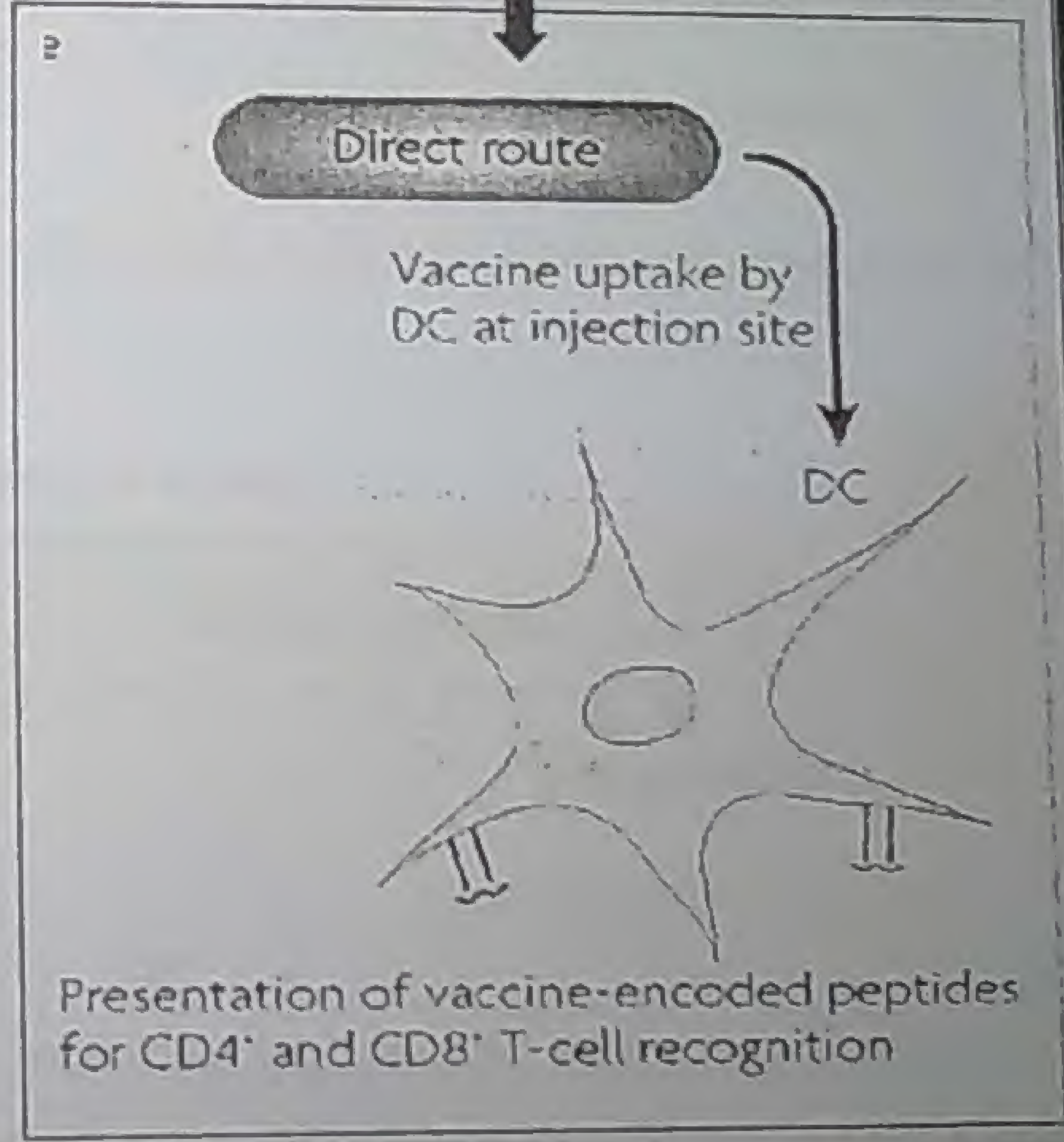
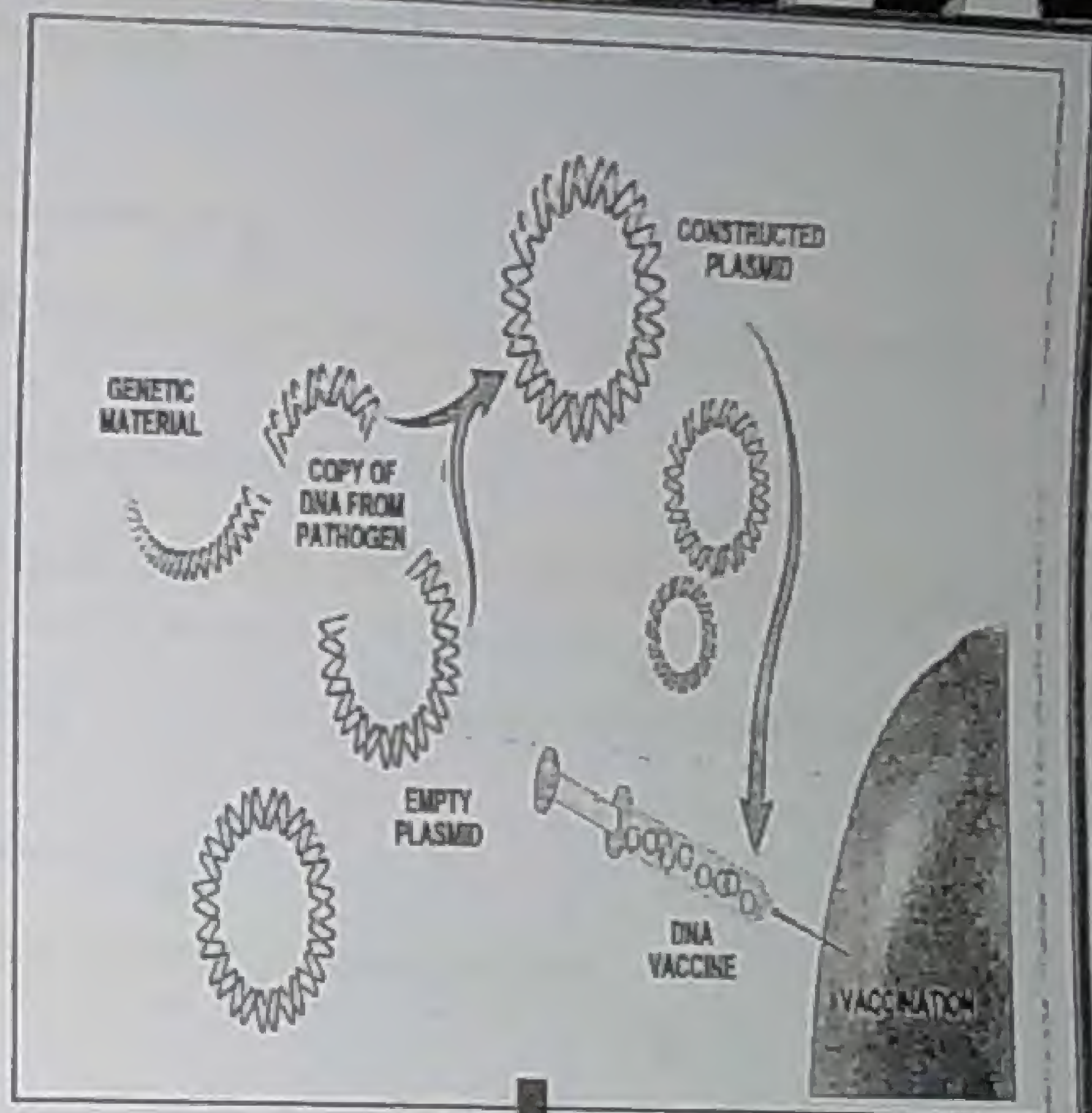
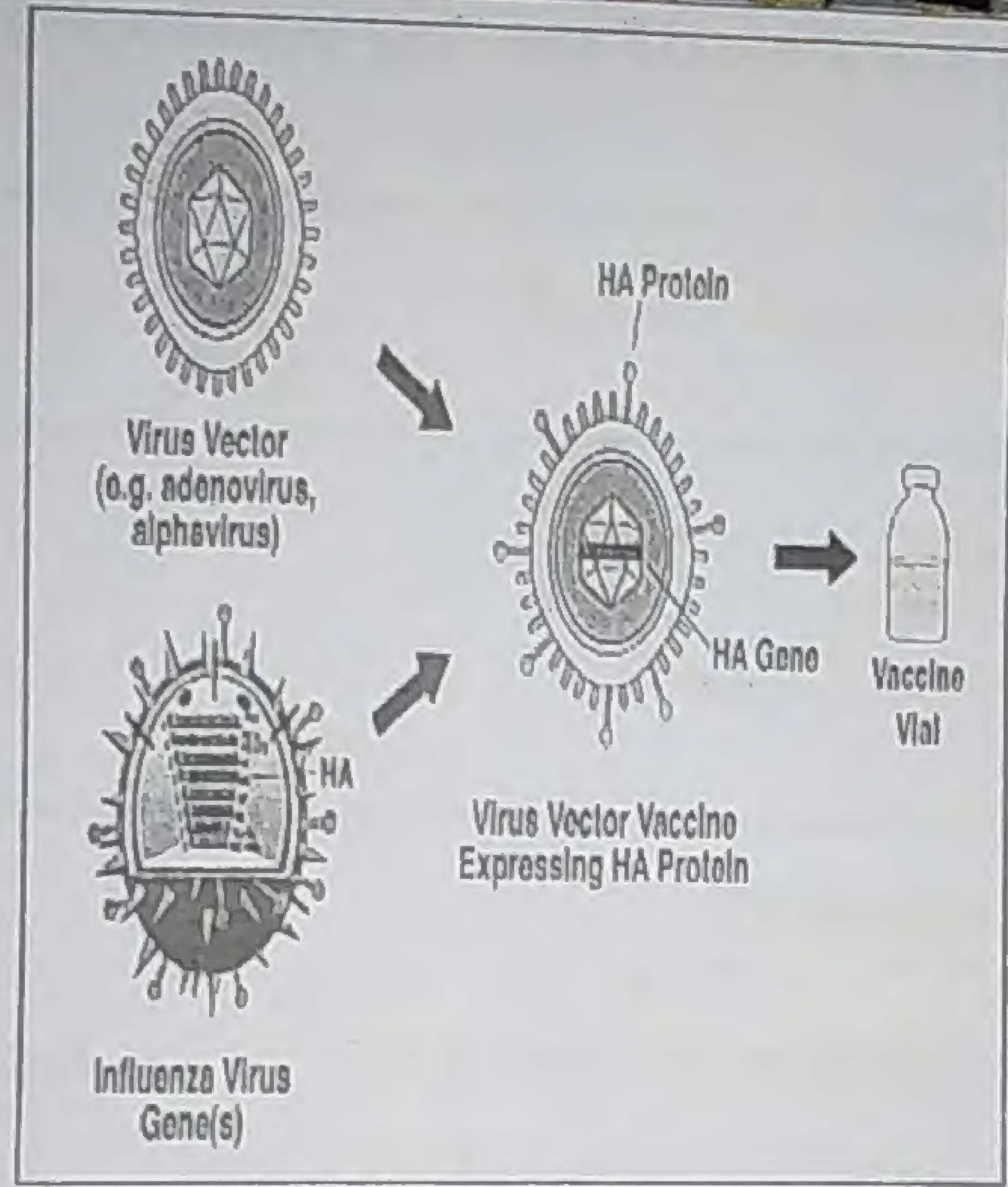
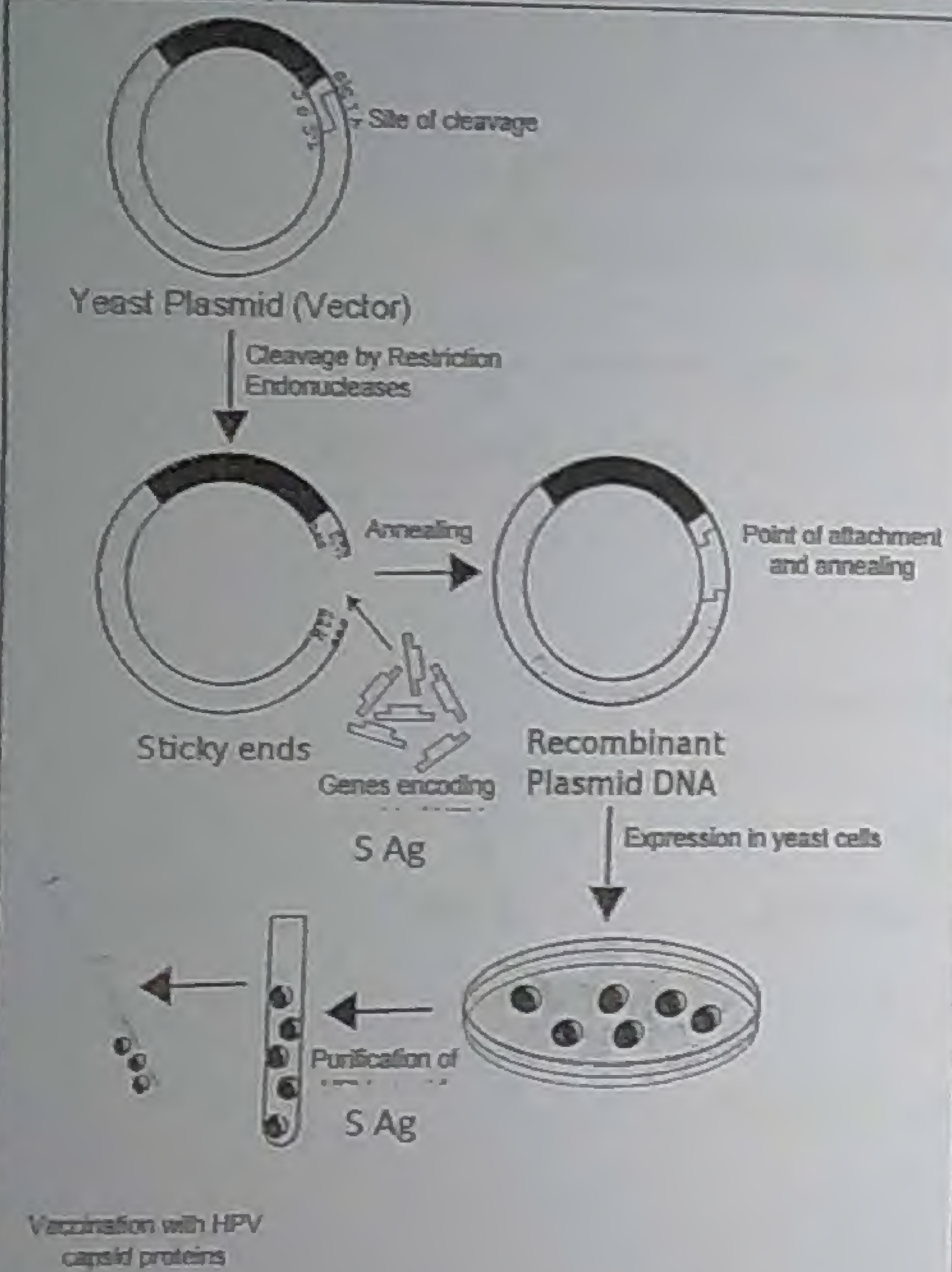
Binds and  
neutralizes virus





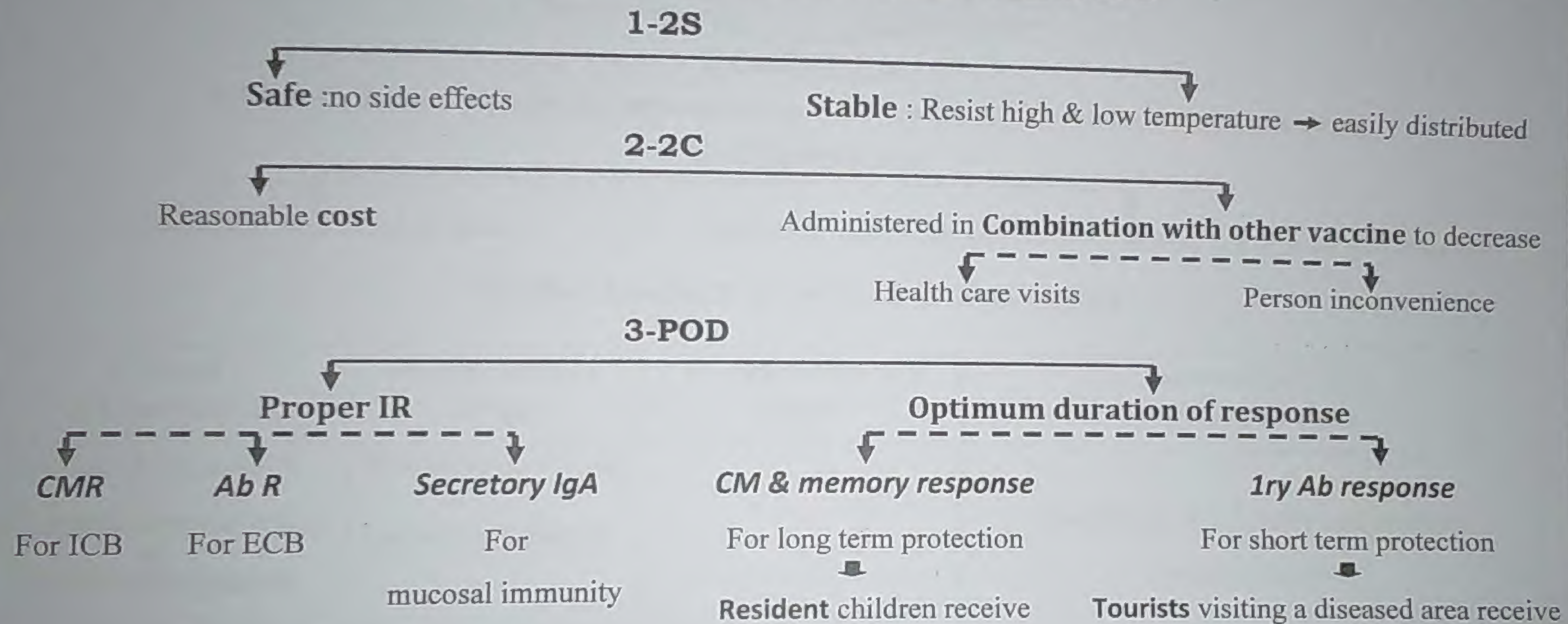
VI-Recombinant vaccines	VII-Recombinant vector vaccines	VIII-DNA vaccine
Gene encoding the most antigenic part in a microbe is identified ↓	Gene encoding major Ag of virulent pathogen is identified ↓	Plasmid containing gene encoding major Ag is injected in the body ↓
Inserted into vector : <b>plasmid</b> ↓	Introduced into vector : <b>attenuated bacteria or virus</b> e.g vaccinia virus ↓	
Recombinant plasmid is inserted into <i>E.coli or yeast</i> ↓	Attenuated org.is injected into <i>host</i> to replicate ↓	<i>Tranfects APCs (dendritic cells)</i> ↓
Genes are expressed with production of Ag ↓	Genes are expressed with production of Ag ↓	Gene is transcribed & translated into Ag (immunogenic protein) ↓
Ags are purified & used as vaccine	Ag ⊕ IR	⊕ strong & long lived humoral & CMIR
	<b>Disadvantages</b>	
	Expression of vector Ags on infected host cells ↓ <i>Killed by CTLs before vector replic.</i> ↓ Vaccination fails	6



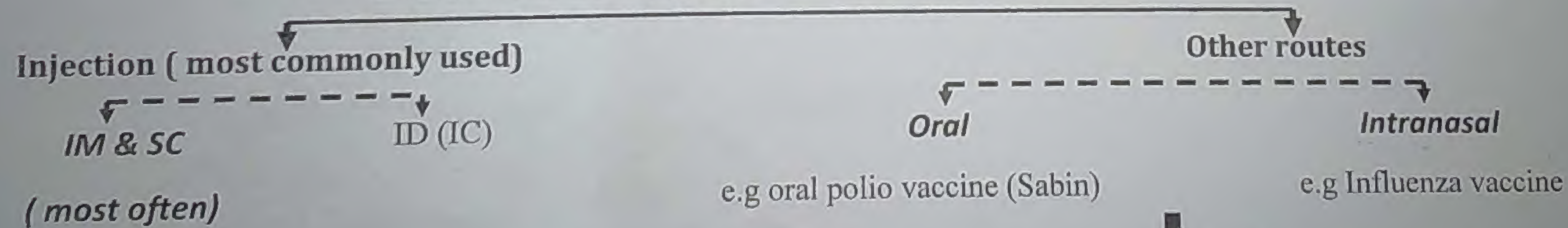




## Properties of an ideal vaccine



## Routes for administration of vaccines





# Adjuvants

## I-Definition

Substances that non specifically enhance IR against a certain Ag when mixed & injected with it

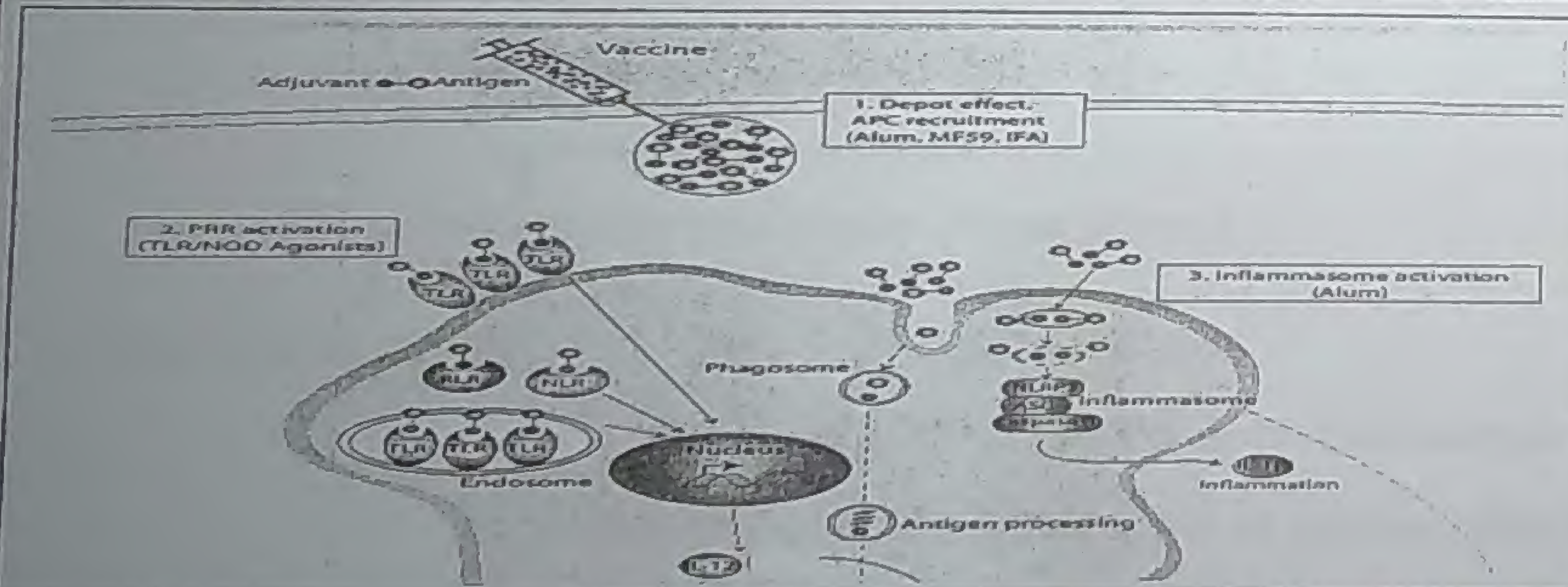
## II-Characters

Chemically irrelevant to Igen

Induce effective Ab (humoral) response, but a weak CM response

## III-Mechanism of action & Examples

i. ↑ local inflammation	ii. Slow release of Ags	iii. ↑ costimulatory signals	Generalised ⊕ of immune cells
Influx of more APCs & ↑ cytokines production ↓ ↑ T&B cell response	Prolongation of Ag persistence (depot)		Cytokines: IL2, 12, IFN $\gamma$ , & GM-CSFs added to vaccines
Aluminium hydroxide added to Diphtheria & Tetanus toxoid			





# Passive Immunization

## I-Passive transfer of Igs

### A-Source

Human or bovine

### B-Indications

Post exposure prevention

e.g rabies, HAV & HBV

Alleviation of  
existing ds

Underlying illness  
preventing administration of vaccine

### C-Types

Specific against certain ds

Hepatitis

A & B

Antitoxins for

♦ Botulism ♦ Tetanus ♦ Gas gangrene ♦ Diphtheria

Non specific

Pooled Igs

ttt of immunodeficiency

### D-Complications

Hypersensitivity reactions (from animal)

Anaphylactic shock

Serum sickness

Transfusion transmitted infections

## II-Passive transfer of CMI

Transfer of CTLs is restricted to persons *sharing MHC class I genes*



## Essay Questions

### 1-Compare & Contrast between:

- i. T cell receptor & B cell receptor
- ii. T cell dependent & T cell independent Ags.
- iii. 1ry & 2ry IR
- iv. Opsonization & ADCC
- v. The 3 pathways of complement activation
- vi. IR to IC & EC pathogens.

### 2-Give an account on

- i. Isotype switch
- ii. Secretory component
- iii. IL4
- iv. Mechanisms of evasion of IR by EC bacteria & parasites
- v. +ve feedback & cross regulation of Th subsets
- vi. Cytokines that stimulate hematopoiesis
- vii. Regulatory proteins of complement components.
- viii. Hapten

### 3-Give a short account on Clinical aspects of complement.

### 4-Enumerate biological activities of complement, give an account on 1 of them

### 5-Define heterophil Ag, mention its practical applications

### 6- Name mechanisms by which Abs eliminate Ag from the body

### 7-Give reason :

- i. T helper cell is important in isotype switch of B cell
- ii. C3b is an important complement component
- iii. Inherited deficiency of complement may lead to angioneurotic edema
- iv. Both interferon & IL 4 influence outcome of class switch.



# Immunology 5

Hypersensitivity

Hypersensitivity



# Diseases associated with humoral immunity

Type I hypersensitivity  
Immediate or anaphylactic

Type II hypersensitivity  
Cytotoxic or cytolytic

Type III hypersensitivity  
Immune complex

## Type I ( Immediate or Anaphylactic ) type

### Mechanism

1-1<sup>st</sup> exposure to Ag → Sensitization

1-Entry of allergen

Any substance that triggers  
allergic reactions  
in the body

Types

- ♦ Pollen , certain foods
- ♦ Drugs : penicillin
- ♦ Serum proteins Albumin  
Antitoxic  
From Animals  
(Against Diphtheria)
- ♦ Bee venom

2-Allergen is taken by APCs & digested

Fragments are presented to Th2 (genetic predisposition is important)

3-Th2 secrete IL4,13 & 5 → ⊕ of B cells → IgE secretion

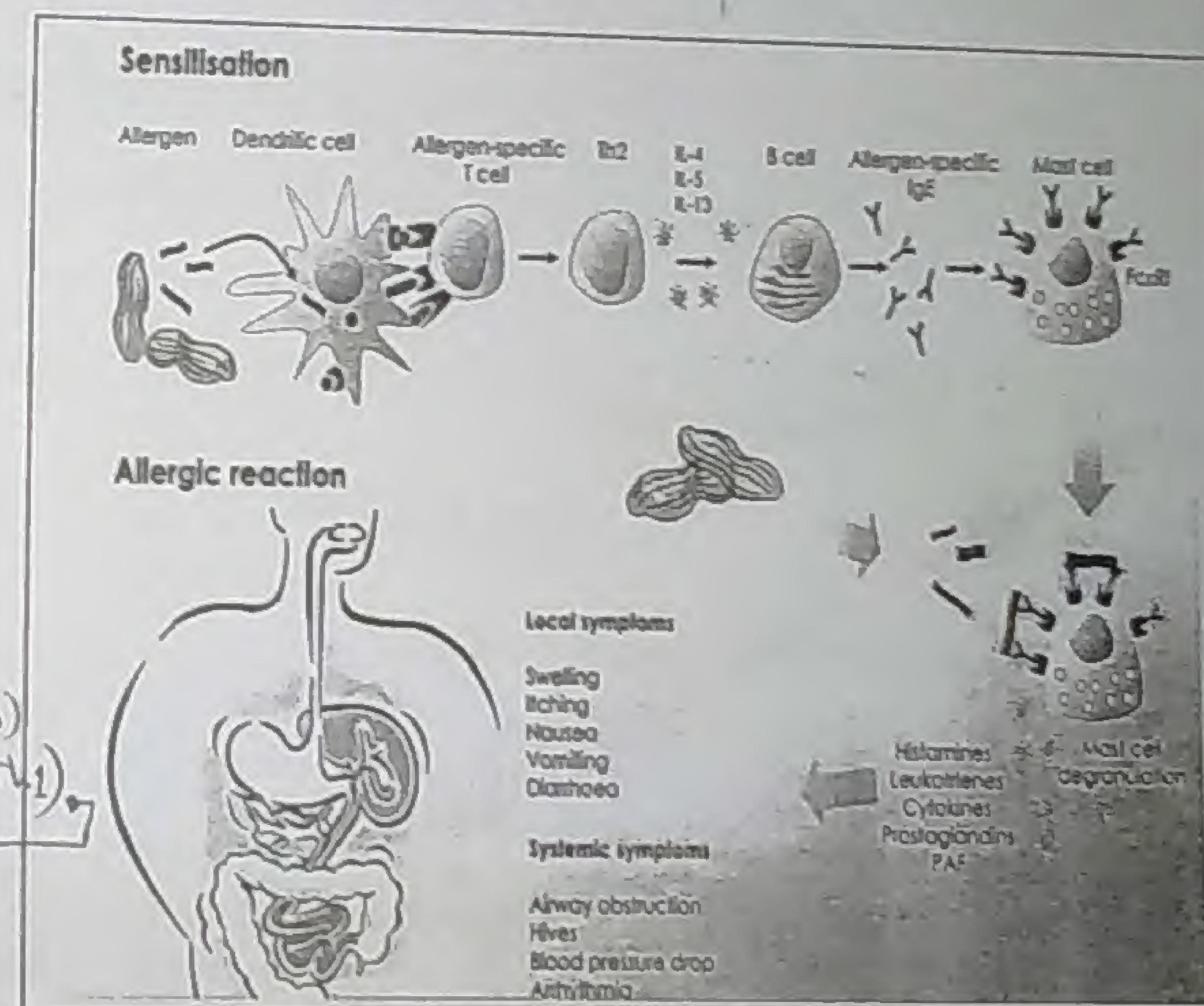
4-Sensitization

IgE enters the circulation

Attaches by its Fc to Fcε R on the surface  
of mast cells & basophils  
Individual becomes *sensitized*

Requires 1w

Millions of IgE mol. are synthesized  
Attach to **thousands of**  
mast cells & basophils



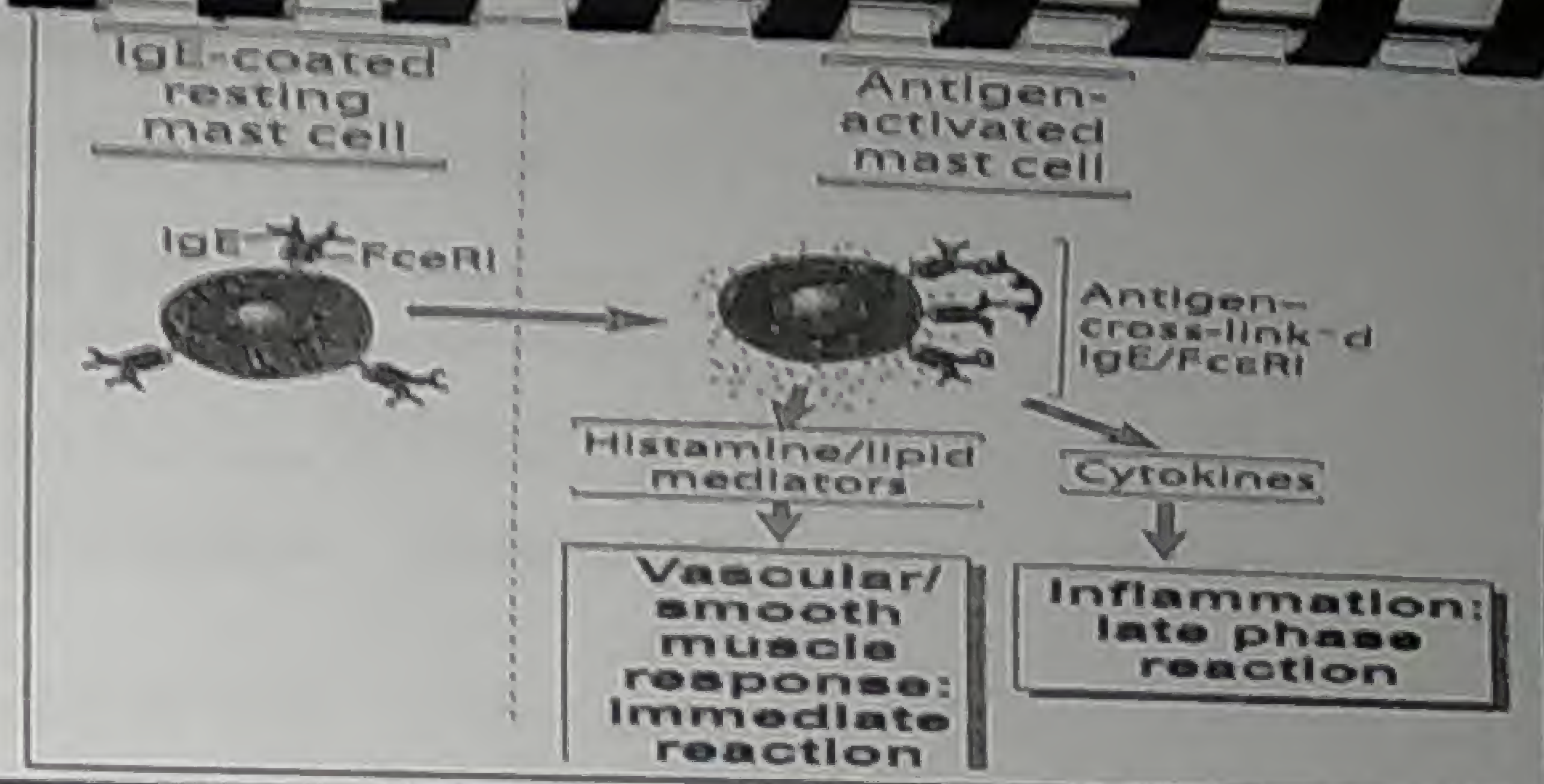


## II - 2<sup>nd</sup> exposure to allergen → Degranulation

On subsequent exposure to the same allergen

↓  
Binds to Fab of IgE Abs cross-linking them

↓  
Degranulation of mast cells in tissues & basophils in blood



	III-Early phase reactions	IV-Late phase reactions <sup>cytokines</sup>
1-Onset after reexposure to Ag	Within minutes	Within hours <sup>na, cu, in, med</sup>
2-Mediators	<p><b>Physiological mediators</b></p> <p>a. Histamine &amp; heparin → 2H</p> <p>b. PGs, proteolytic enzymes &amp; PAF <sup>Platelet Activating Factor</sup></p> <p>c. Leukotrienes &amp; ECF-A <sup>More Histamine</sup>  <small>→ eosinophil chemotactic F</small>  <small>= F Anaphylaxis</small></p>	<p><b>Cytokines</b> <sup>(synthesized after degranulation)</sup></p> <p>TNF α &amp; IL 3 <sup>(not affected)</sup>      IL 4, 13 &amp; 5</p> <p>Recruitment of neutrophils, eosinophils &amp; Th2</p>
3-Effects	<p>a. <u>VD</u> &amp; ↑ capillary permeability</p> <p>b. Sm contraction &amp; ↑ mucus secretion <sup>In bronchi &amp; SI</sup></p> <p>c. ⊕ of nerve endings in skin</p> <p>Itching      Pain</p>	<p>a. TNFα      IL5</p> <p>⊕ neutrophils      ⊕ eosinophils</p> <p>↓</p> <p>Release proteases</p> <p>↓</p> <p>Tissue damage</p> <p>b. Th2 produces more IL4, 13 &amp; 5</p> <p>↓</p> <p>Exacerbation <sup>تفاقم الحالة</sup></p>

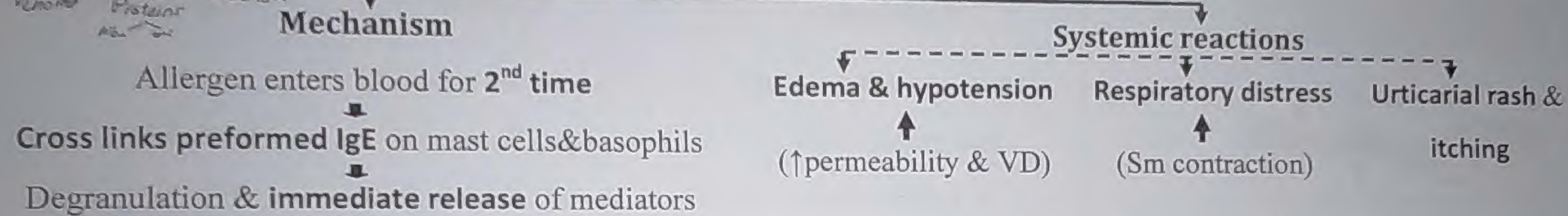


## Clinical presentations

In respiratory passages, intestinal walls & skin (sites of mast cells)

IV exposure of  
Bee venom    Serum Protein    Penicillin

### I-Systemic anaphylaxis (fatal within few minutes)



### II-Localized anaphylaxis : atopy (atopia = extraordinary)

RT → A- Airborne allergens → Allergic rhinitis & bronchial asthma

	Allergic rhinitis	Bronchial asthma
1-Allergens	✓ i.Plant pollen    ii.Animal hair & dander	iii.House dust    iv.Fungal spores    v.Mites <sup>العث</sup>
2-Mechanism	<p style="text-align: center;">Degranulation of mast cells in:</p> <div style="display: flex; justify-content: space-between;"> <div>MM of eye &amp; upper RT</div> <div>Lower RT</div> </div>	
3-Symptoms	i.Red itchy tearing eyes ii.Congested nasal passages iii.Coughing & sneezing	<p style="text-align: center;">Difficulty in breathing &amp; wheezy chest due to:</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>Sm contraction</p> </div> <div style="text-align: center;"> <p>Bronchial narrowing by:</p> <p>i.VD &amp; ↑ permeability</p> <p>ii. ↑ mucus</p> </div> <div style="text-align: center;"> <p>Alveolar overdistension with fluids &amp; mucus</p> </div> </div>

GIT → B-Food & Drug allergens (ingestion)

Affect GIT → Local reactions

Abdominal cramps, vomiting & diarrhea

Absorbed in blood

Reach skin

↓

Urticarial rash

3

Reach lungs

↓

Asthmatic attacks



# Diagnosis

## I-Allergy skin test → determine causative allergen

Test allergen

- Pollens.
- Grasses & molds
- Cat dander
- Food
- Penicillin (before inj.)

Method

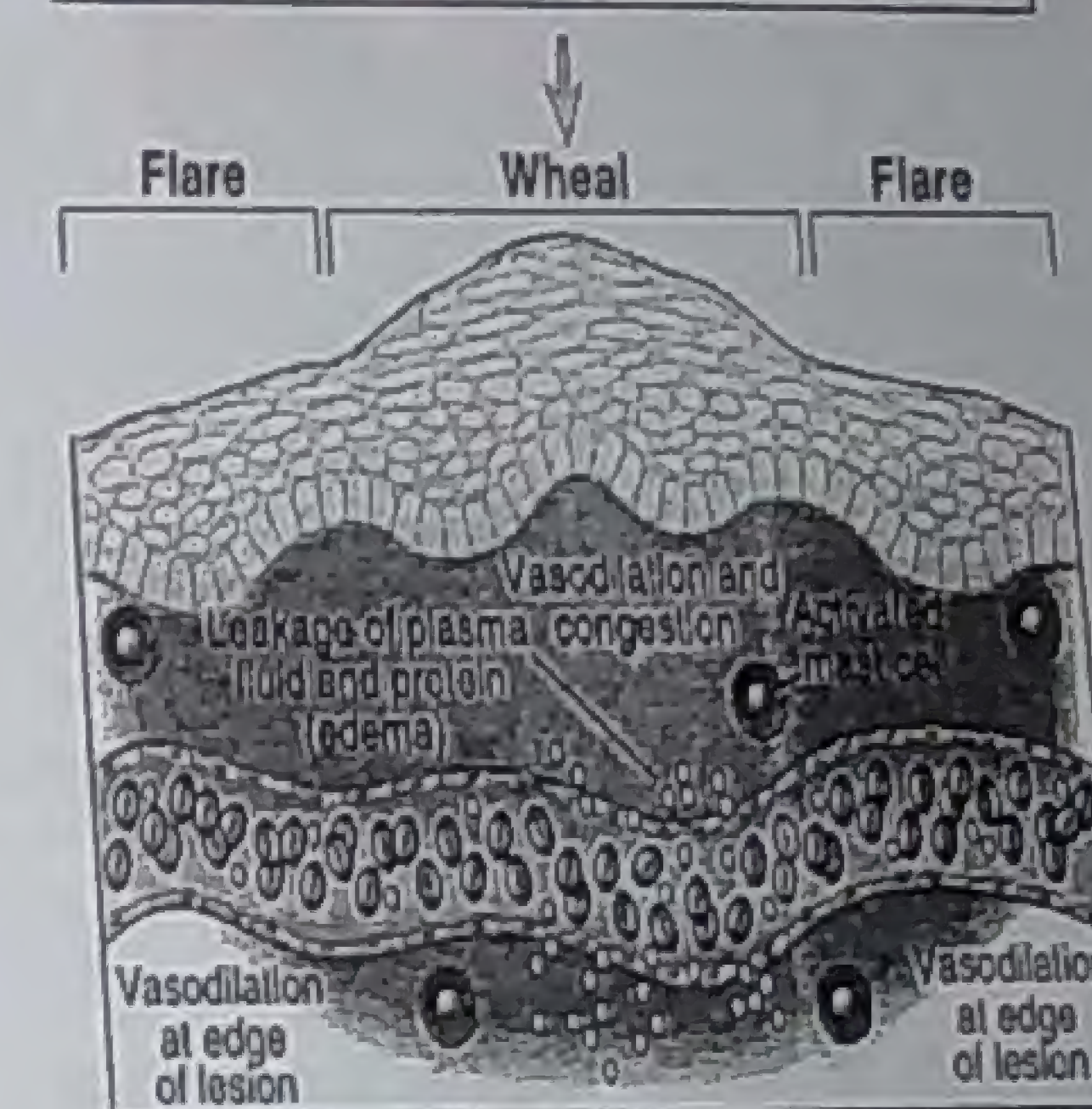
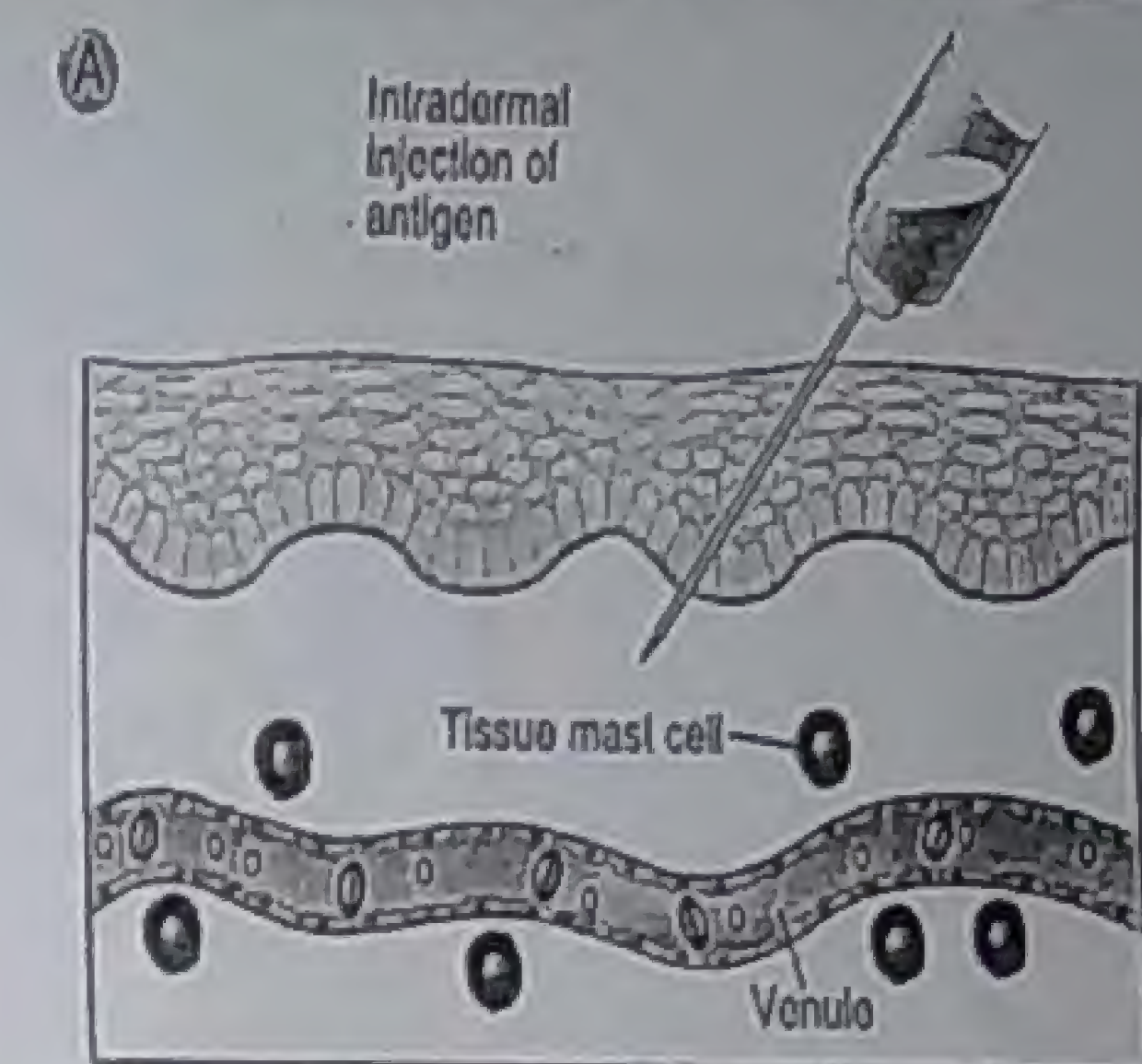
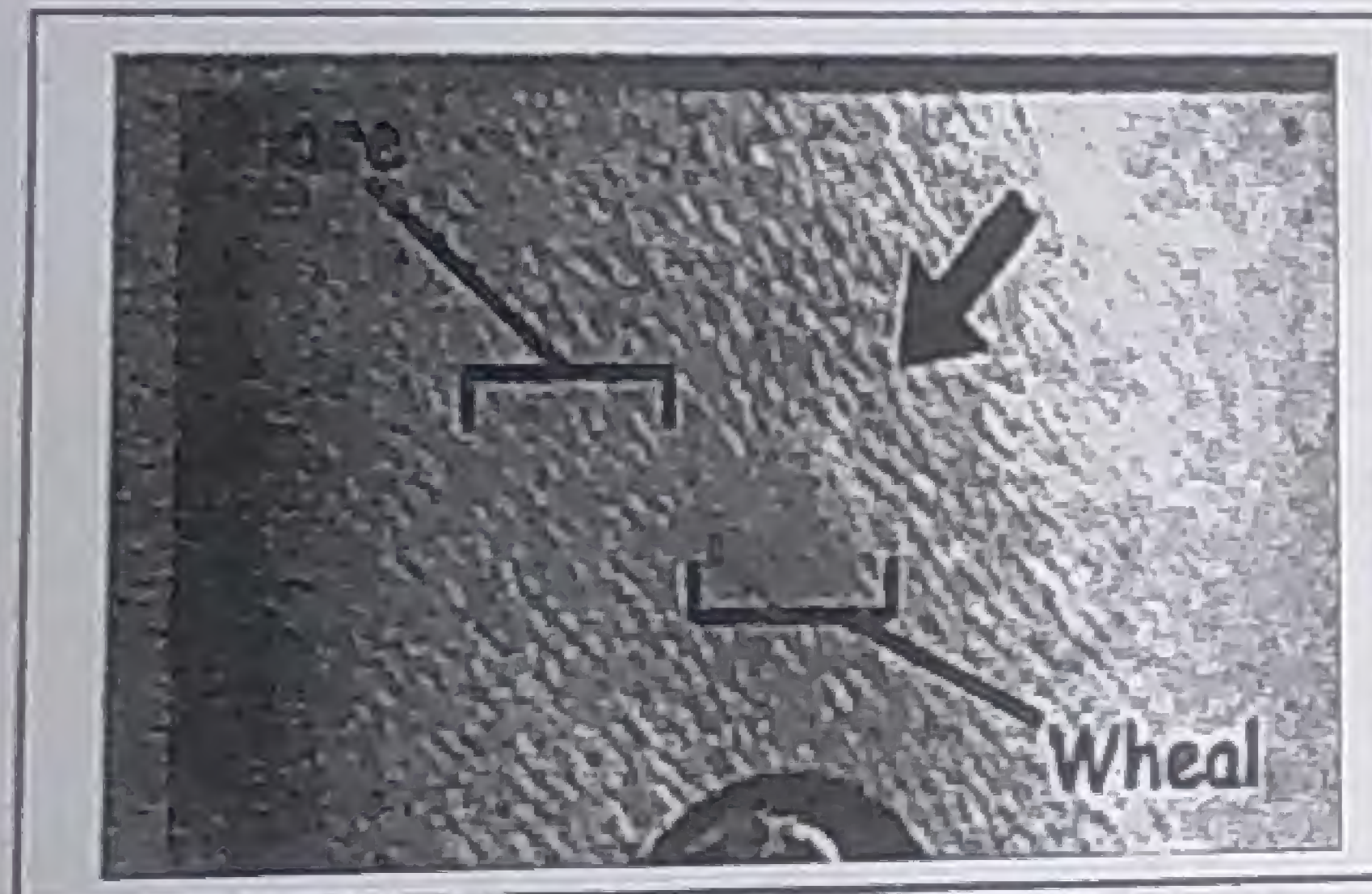
Pricking the skin in forearm & back with a sterile lancet

+ve result

Wheel & flare reactions within 15-20 min (small circles of itchy inflammation like mosquito bite)

♣ Based on its size, sensitivity is assessed as:

- Mild
- Moderate
- Severe



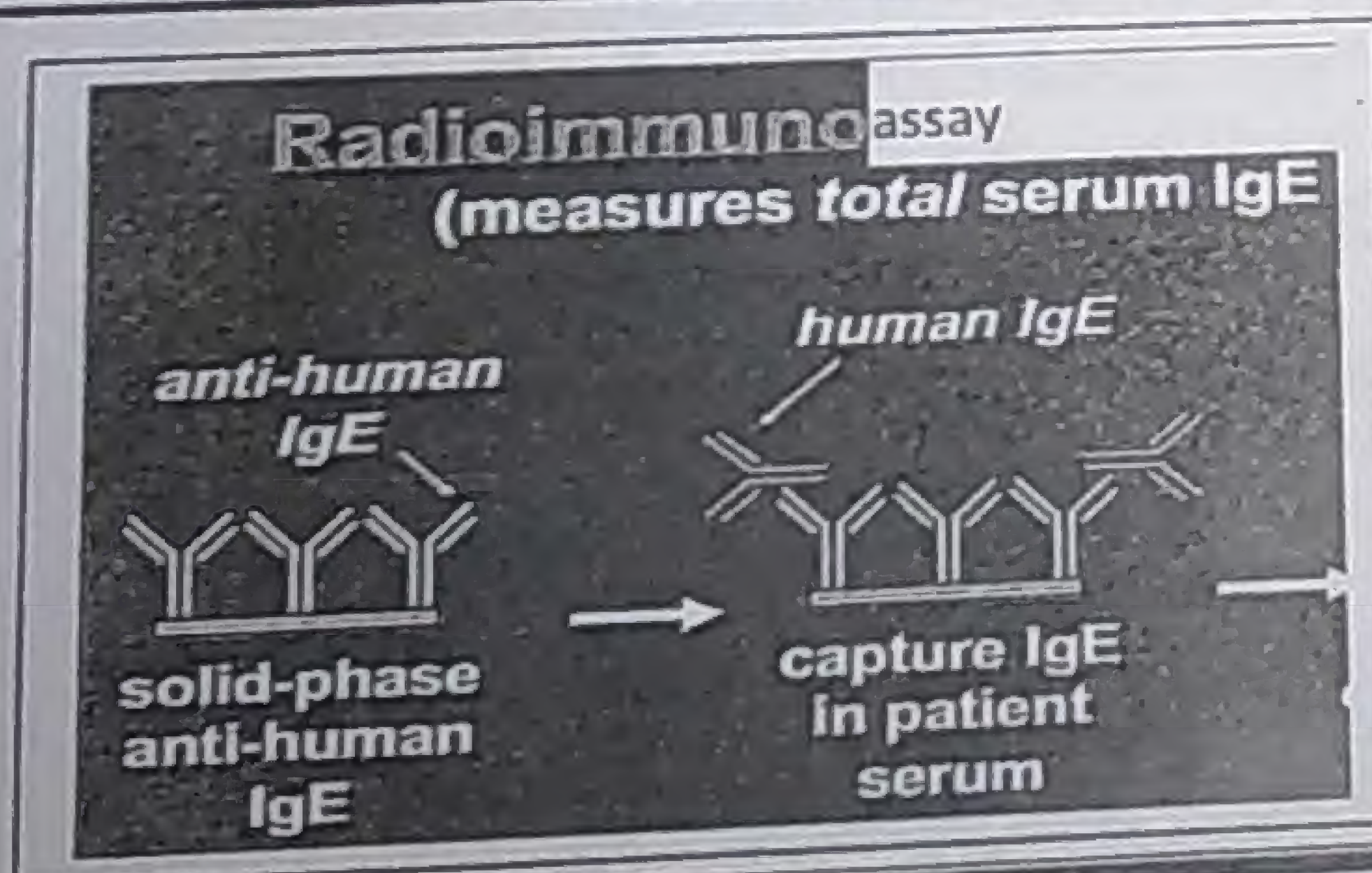
## II-Allergy blood tests → measurement of serum IgE

Total IgE :

by RIA

(Radioimmunoassay)

↑ in some allergic pts

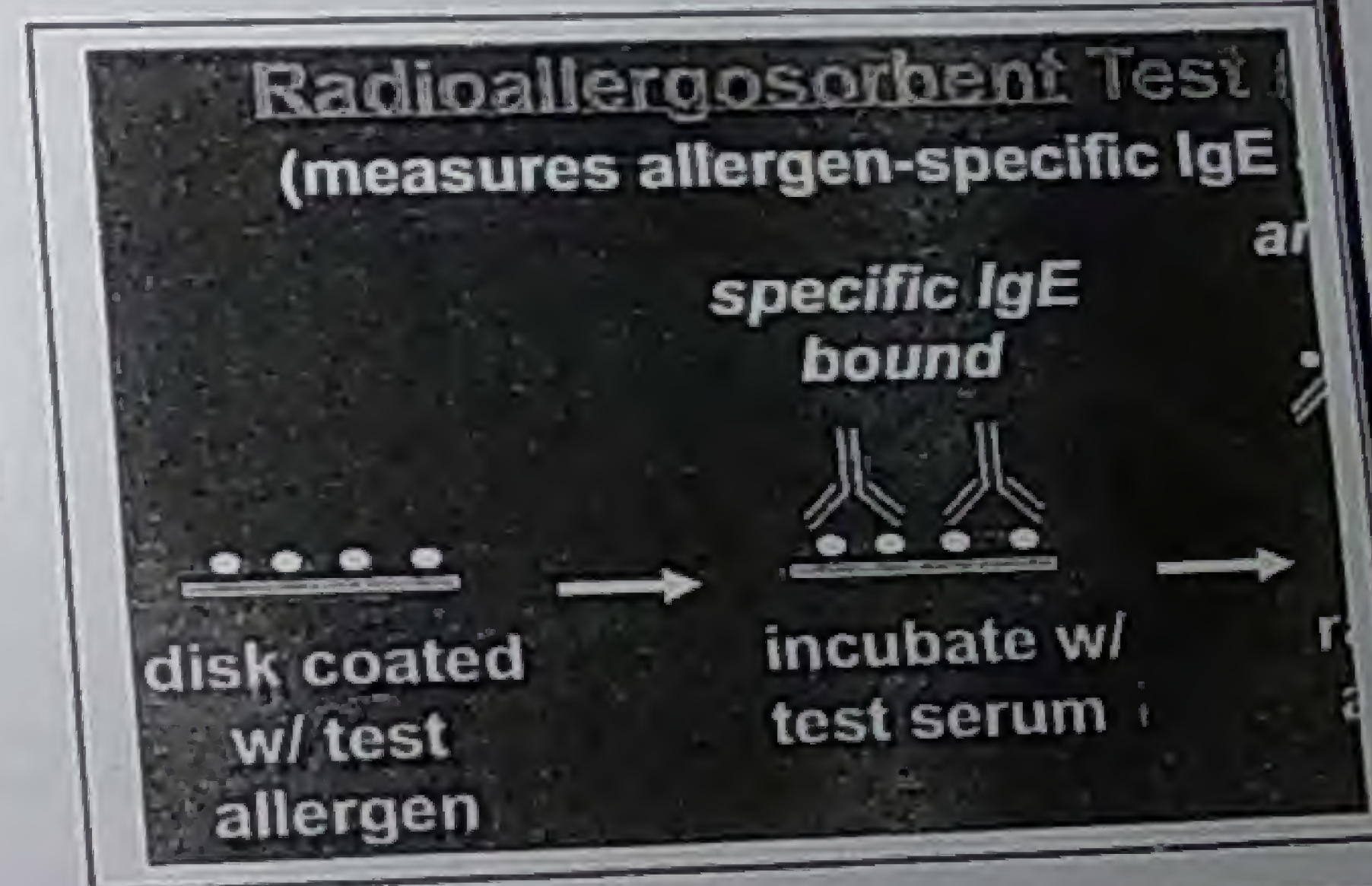


Specific IgE :

by RAST

(Radioallergosorbent Test)

Specific against certain allergen





# Management

## I-Identifying & avoiding allergen ( if possible)

The *most effective* way of prevention

## II-Drugs

Relieve symptoms or prevent release of chemical mediators

Epinephrine	Corticosteroids	Mast cell stabilizers	Anti
(life saving)	↓ inflammation	(Na chromoglycate)	histaminics
Relaxes Sm & constricts BVs	↓ all immune cells	⊖ mast cell degranulation	

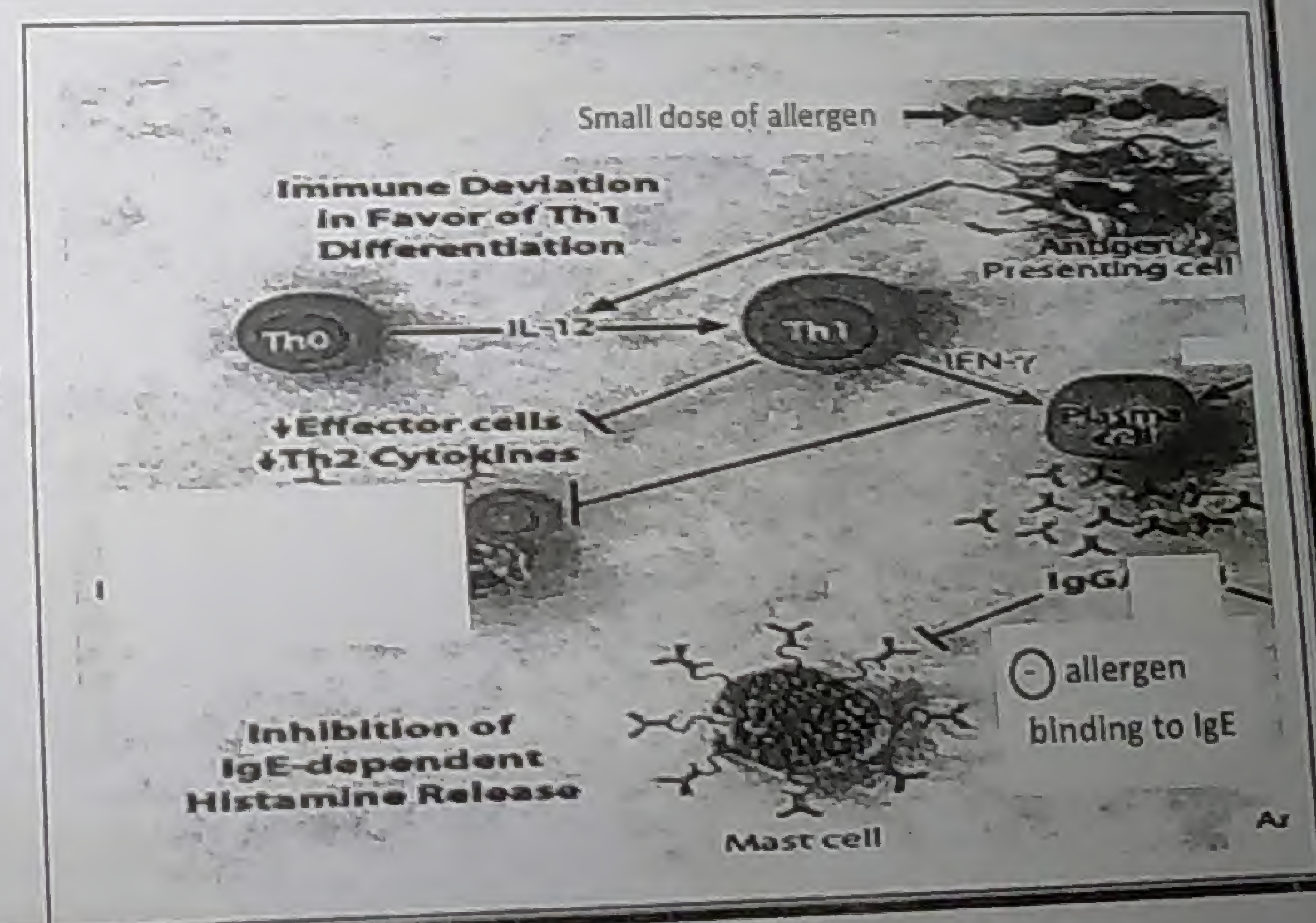
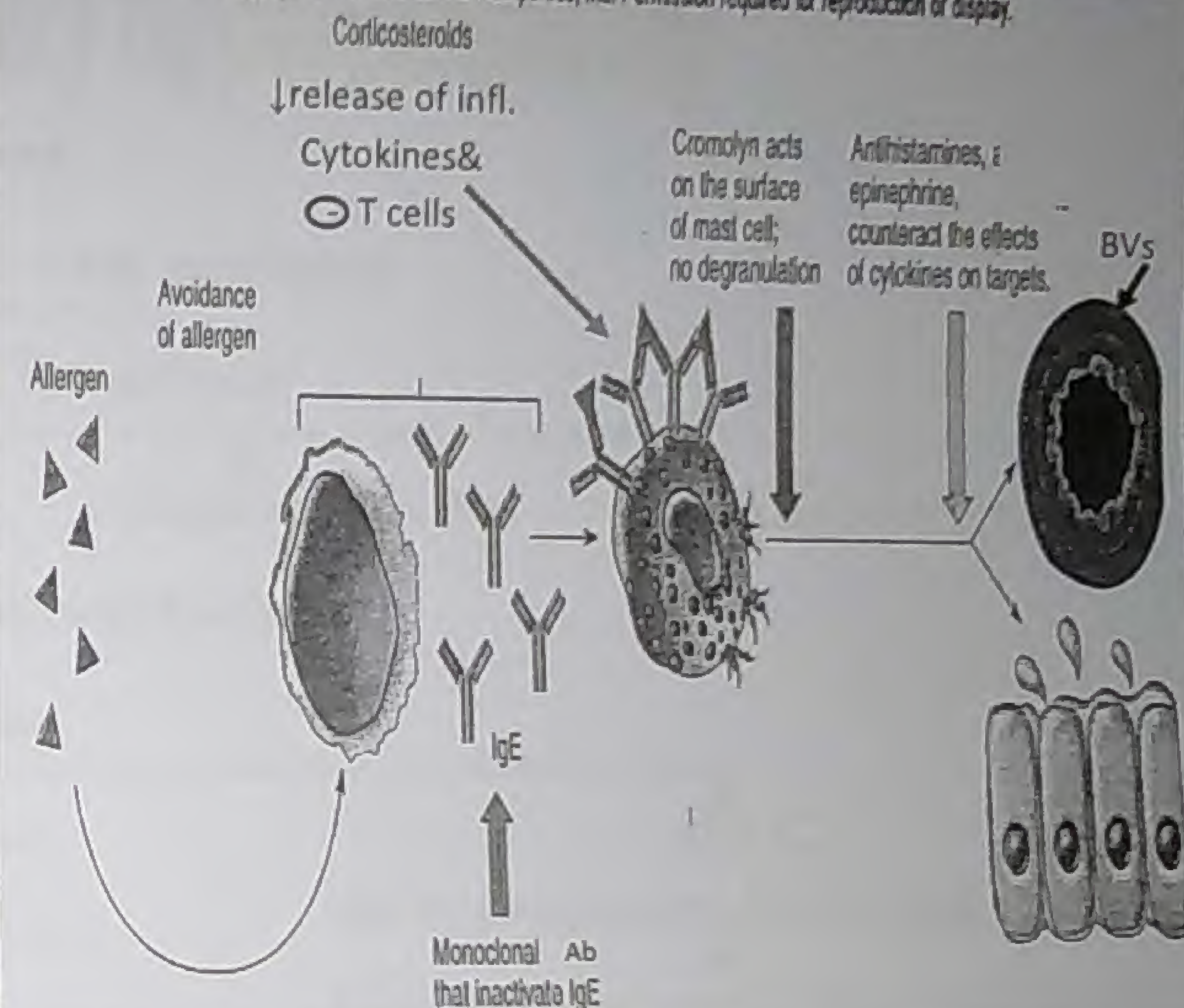
## IV-Monoclonal Abs : Anti IgE

Prevent IgE from binding to mast cell

## IV-Allergen immunotherapy : desensitization

Indication	Method
Failure of medications to control allergy symptoms	Gradually ↑ allergen doses are injected SC (Blocking Antibodies) ⊕ production of IgG rather than IgE Capture & neutralize Ag before reacting with IgE bound on mast cells ( prevent crosslinking)

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# Type II ( Cytotoxic or cytolytic ) hypersensitivity

## Mechanism

### 1-IgG or IgM against Ag on cell surface

Endogenous

Due to failure of tolerance

Exogenous

Hapten (drug) or organism

Allogenic RBCs Ags

Allogenic graft cells

### 2-Ab binds to Ag on cell surface

### 3-Lysis of cell by

Complement activation ( classical pathway)

MAC ( C5b6789)

create pores in cell

Opsonization

Phagocytes bind to

IgG or C3b on cell

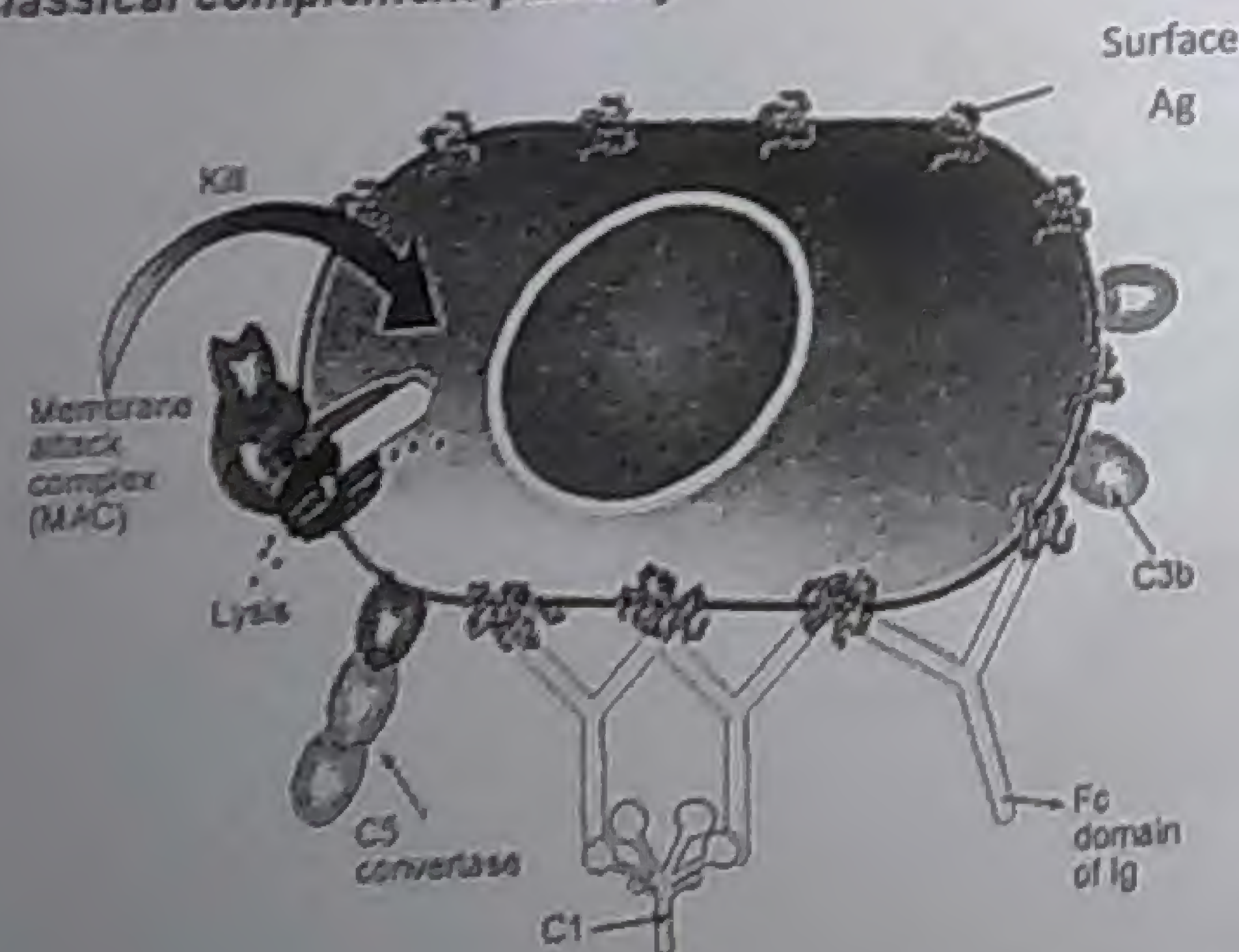
ADCC

NK or phagocytes bind to IgG on cell

Discharge their perforins, granzymes & proteolytic enzymes

### Type 2 - antibody-dependent cytotoxicity

Figure 2a: Classical complement pathway



### Opsonization and phagocytosis

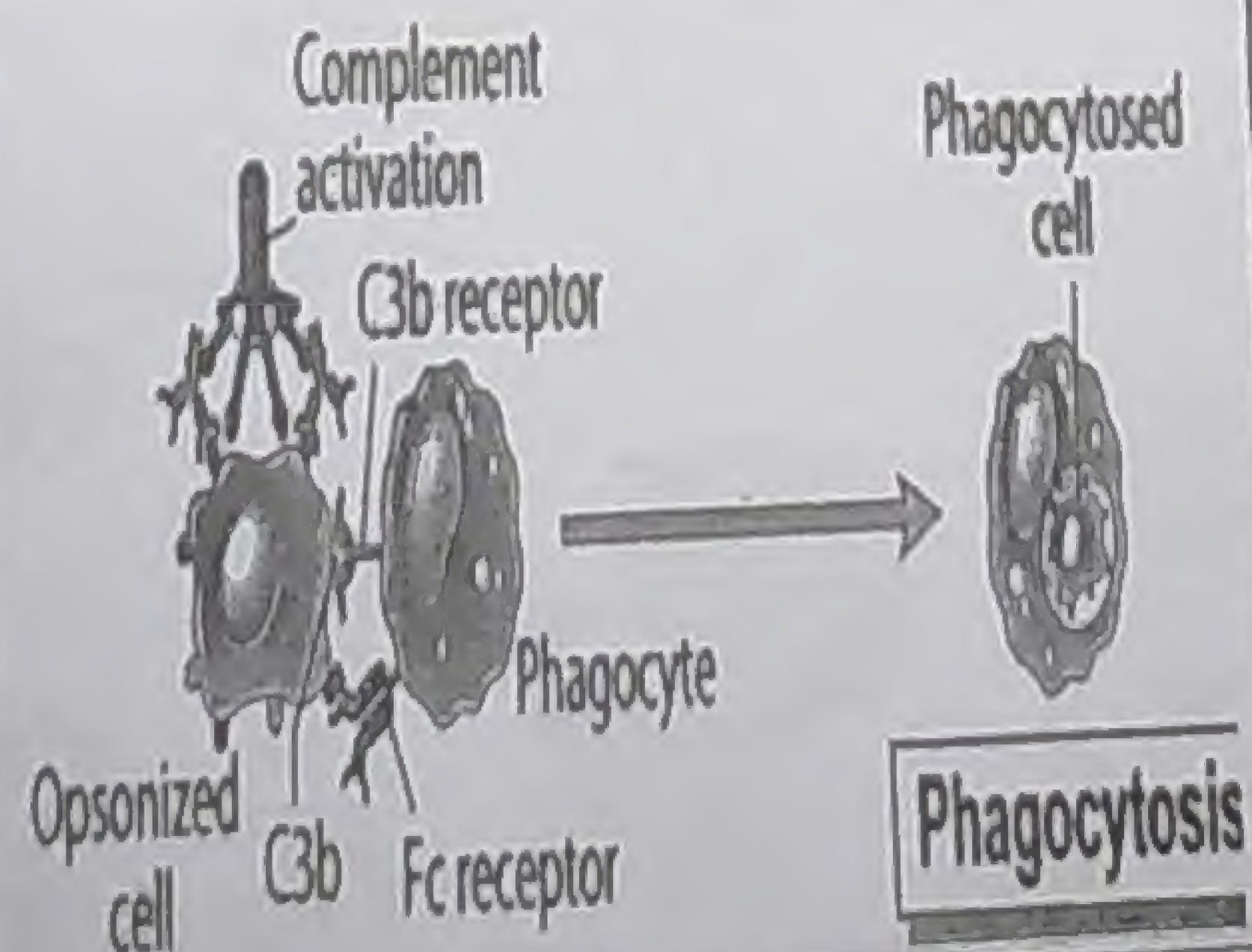
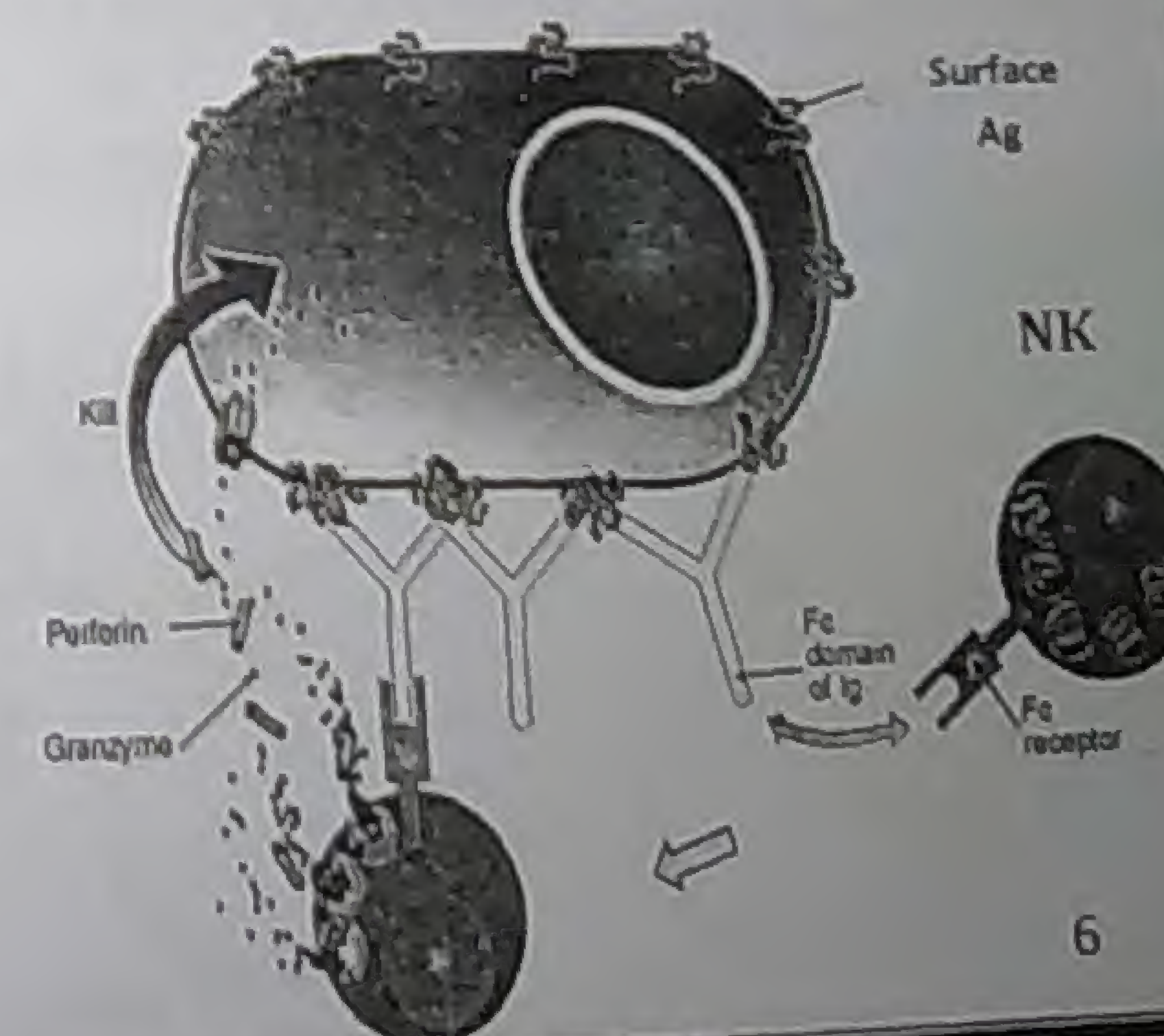


Figure 2b: Antibody dependent cell cytotoxicity (ADCC)





# Clinical syndromes

## Immune destruction of blood elements

Allohemolysis

Autohemolysis

Autolysis of Granulocytes & Platelets

## Other syndromes

Exogenous Ags

Endogenous Ags

## I - Allohemolysis

### ABO compatibility

(commonest cause of transfusion reactions)

*ABO Ags are allogenic*

(differ between persons)

If **A+ve** person  
is transfused with

**B+ve** RBCs

*Natural antiB IgM*  
rapidly hemolyse RBCs

in circulation

*by complement*  
(rapid IV hemolysis)

### Rh incompatibility (Rh factor or D Ag)

Mechanism

*Fetal Rh+ve RBCs leak into Rh-ve mother  
circulation during birth of 1<sup>st</sup> child*

*Sensitizes mother to produce IgG*

*Cross placenta in subsequent pregnancies*

*Destroy fetal RBCs*

*(Erythroblasts released from fetus  
to compensate lysed cells)*

*Stillbirth or baby with jaundice*

*↳ (Immune erythroblastosis Fetalis) •*

Prevention

*AntiD injections*

*Given to mother*

*within 72 hrs*

*of 1<sup>st</sup> delivery*

*of RH+ve baby*

*Destroy any*

*leaking fetal RBCs*

*to mother blood during delivery*

*No ⊕ of mother IS*

Treatment

*Exchange*

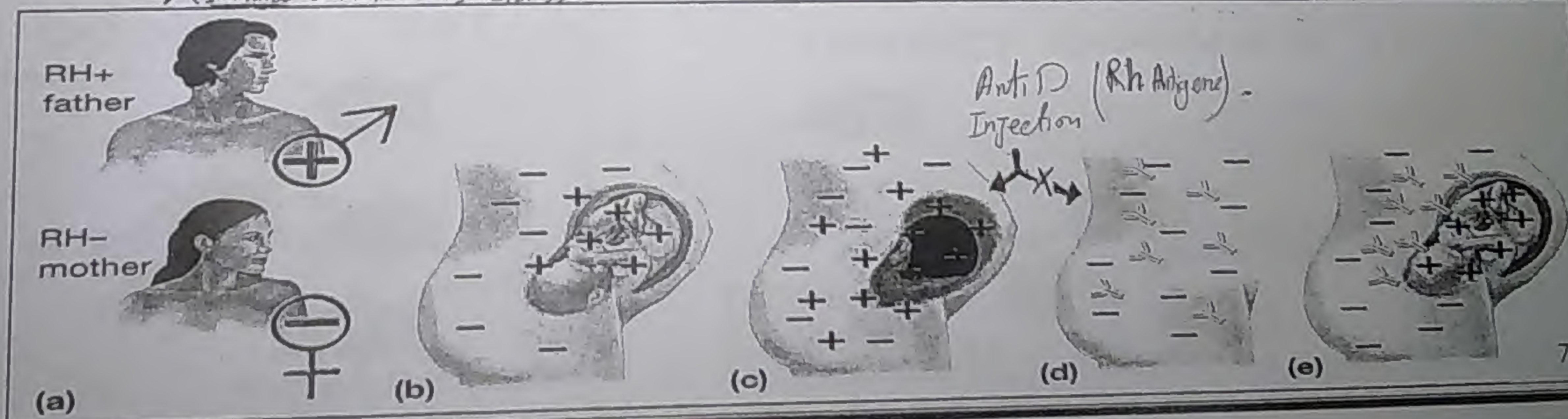
*transfusion*

*of fetal RBCs*

*with RH-ve*

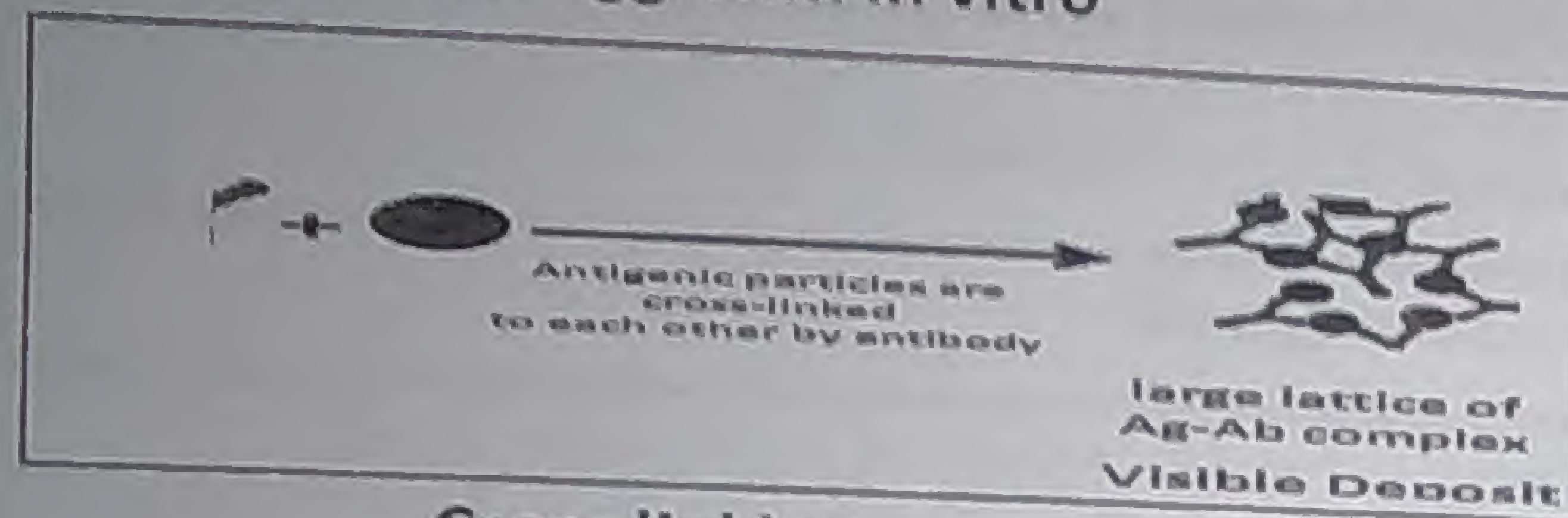
*cells*

*to avoid its destruction  
by maternal Antibodies*





Normal agglutin. in vitro



Cross linking

Incomplete Rh Abs



No cross linking

Coombs' reagent (Antihuman Igs)



Bind to Fc of human IgG

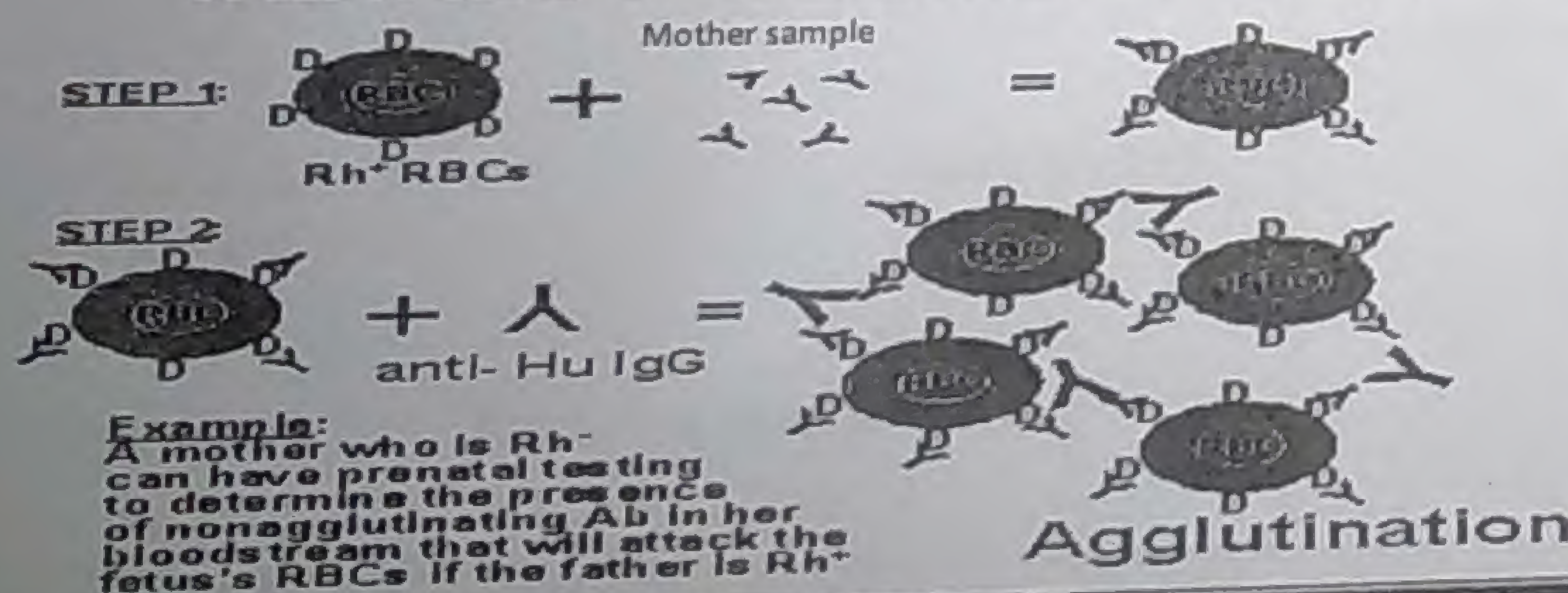
Diagnosis : Coombs' test

Aim : Detect incomplete Rh Abs (IgG):

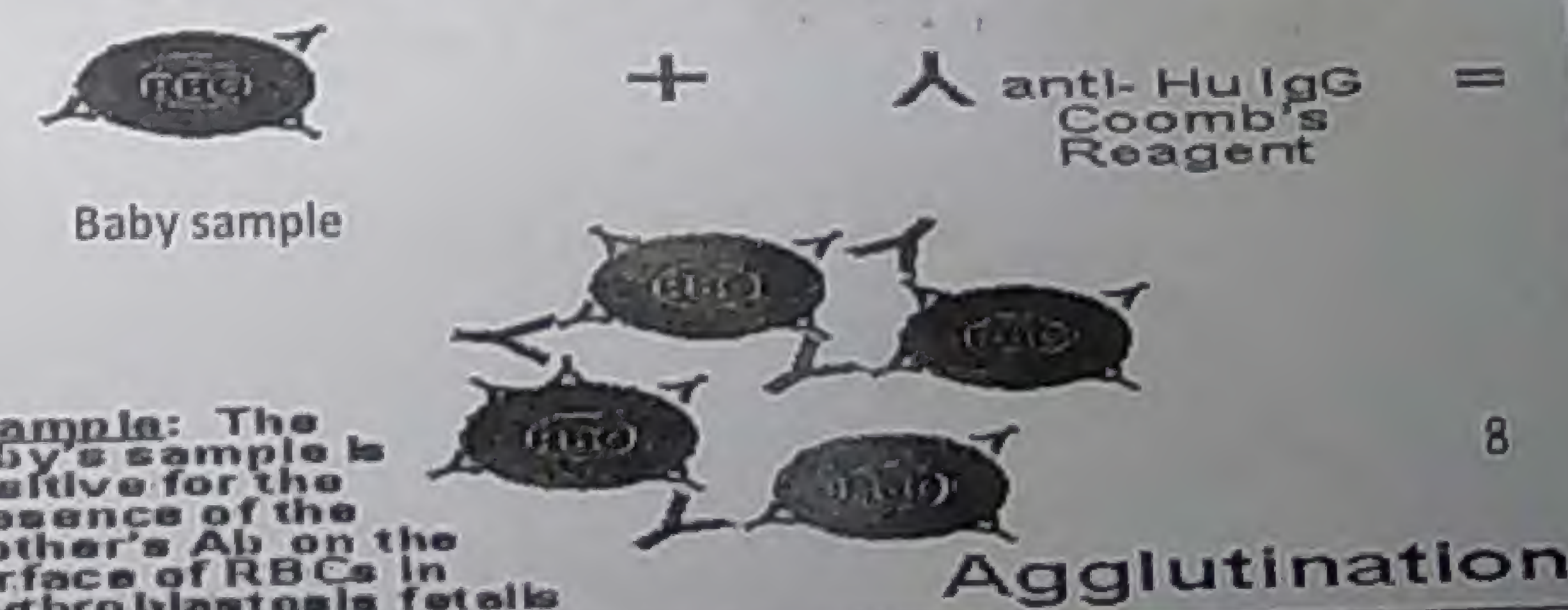
They coat Rh+ve RBCs , but *can't bridge* between them to cause agglutination  
Cause agglutination only after addition of Coombs' reagent (antihuman globulin)

	Indirect coombs'test	Direct coombs'test
1-Uses	Detect free Rh Abs in serum of mother	Detect <i>Rh Abs coating RBCs</i> in serum of <i>newborn</i>
2-Method	i. Blood sample from mother ii. Add Rh+ve RBCs + Coombs' reagent	i. Blood sample from newborn ii. Add Coombs' reagent
3-+ve result	RhAbs coat Rh+ve RBCs Agglutination by Coombs' reagent	<i>RBCs coated with RhAbs</i> Agglutination by coombs' reagent

### INDIRECT COOMB'S TEST



### DIRECT COOMB'S TEST





## II-Autoimmune hemolysis , thrombocytopenia or granulocytopenia

Production of Abs against *pt own* RBCs, granulocytes or platelets

### Exogenous Ags

### Endogenous Ags

Drug metabolite (hapten) bound to protein Ag on cell surface (carrier)

Abs are cytotoxic to cell-drug complex

Hemolytic anemia

Granulocytopenia

Thrombocytopenic purpura

♦ Penicillin

Quinidine

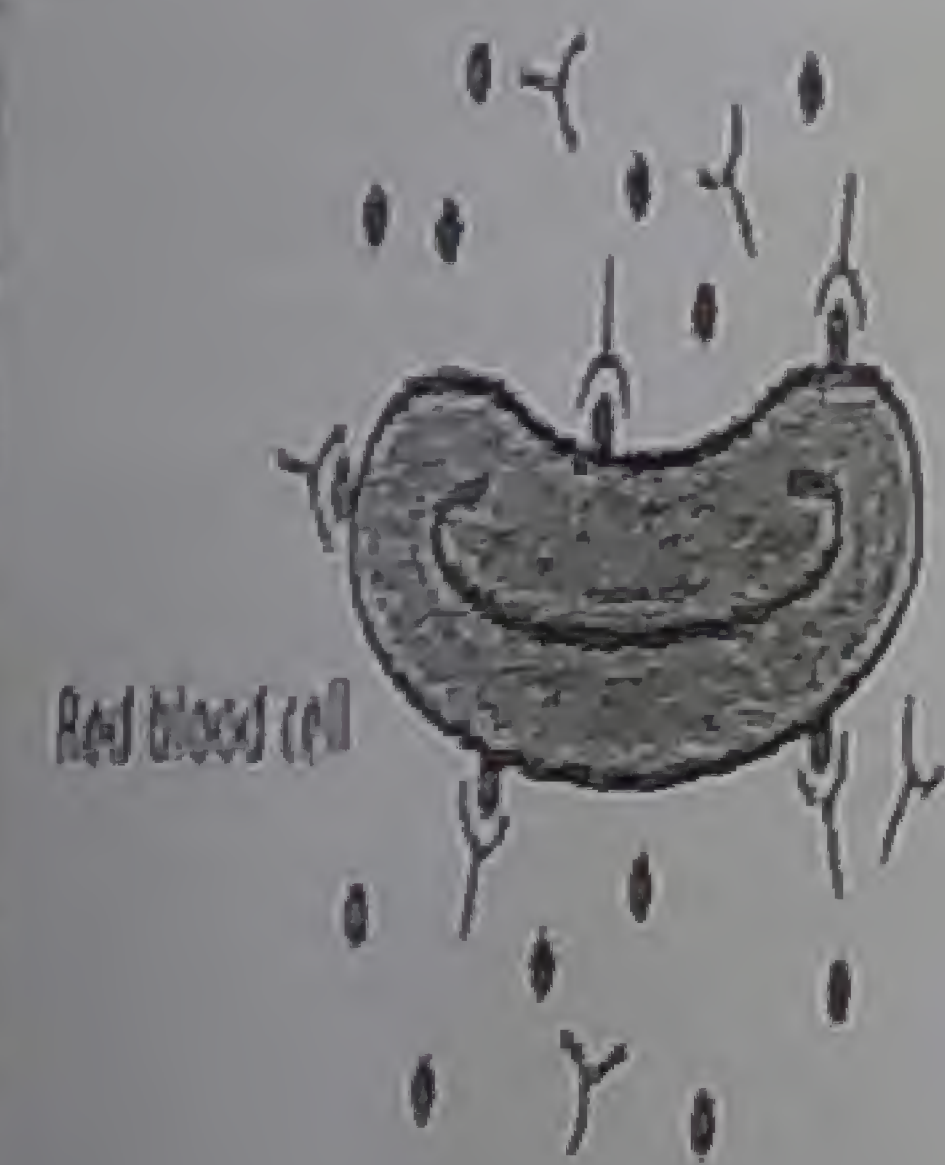
Acetaminophen استيك منه فيه

♦ Chlorpromazine

(antiarrhythmic)

( analgesic)

(antipsychotic)



Hapten mechanism  
(e.g. penicillin)

Penicillin

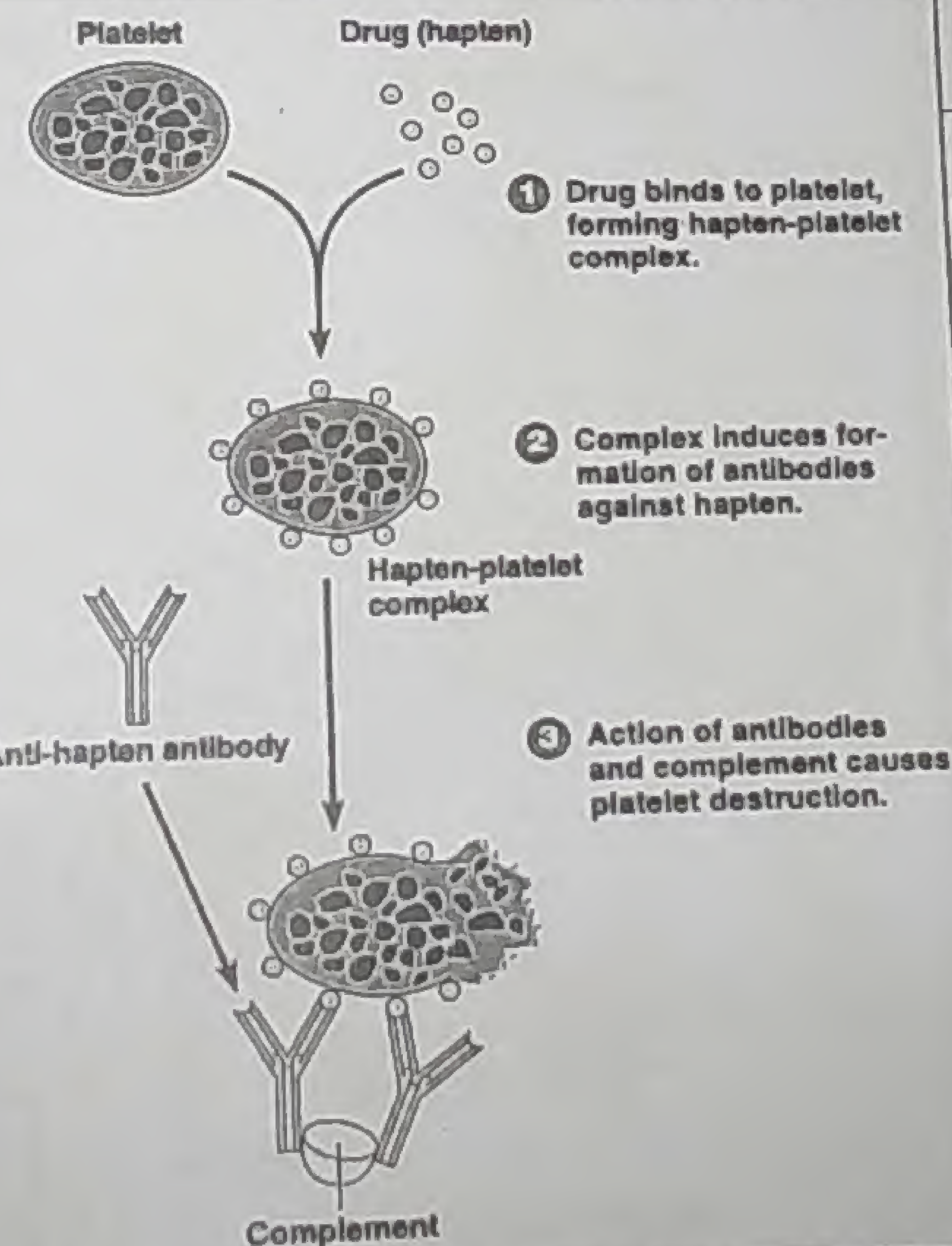
Antibody

Pentamer IgM

Quinine



Granulocytopenia  
e.g. quinidine



Hemolysis through  
Membrane Attack Complex.



Hemolysis  
by opsoniz.





### III - Other clinical syndromes

#### Endogenous

##### Antireceptors (type V hypersensitivity)

Non-cytotoxic AB  $\leftarrow$  Abs **block ability of receptor**

to bind with its **natural ligand**  
without  $\oplus$  complement

$\oplus$  of receptor signaling

**Grave's ds**

IgG binds &  $\oplus$  TSH receptors

on thyroid cells

Hyperthyroidism

*Grave's diseases*

$\ominus$  of receptor signaling

**Myasthenia Gravis**

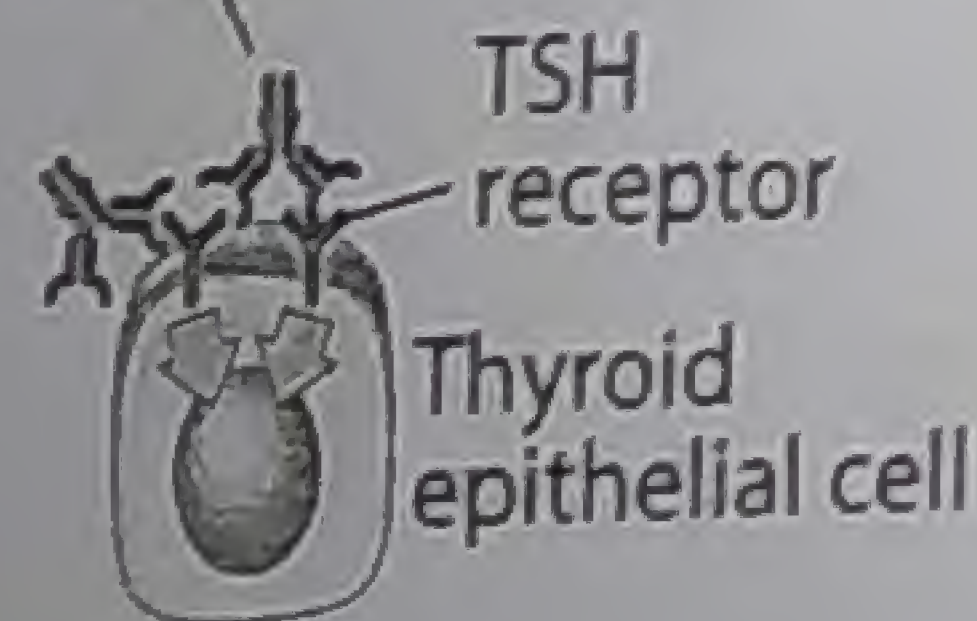
IgG binds &

$\ominus$  acetylcholine receptors

Progressive muscle weakness

##### Abnormal physiologic responses without cell/tissue injury

Antibody against TSH receptor



Thyroid hormones

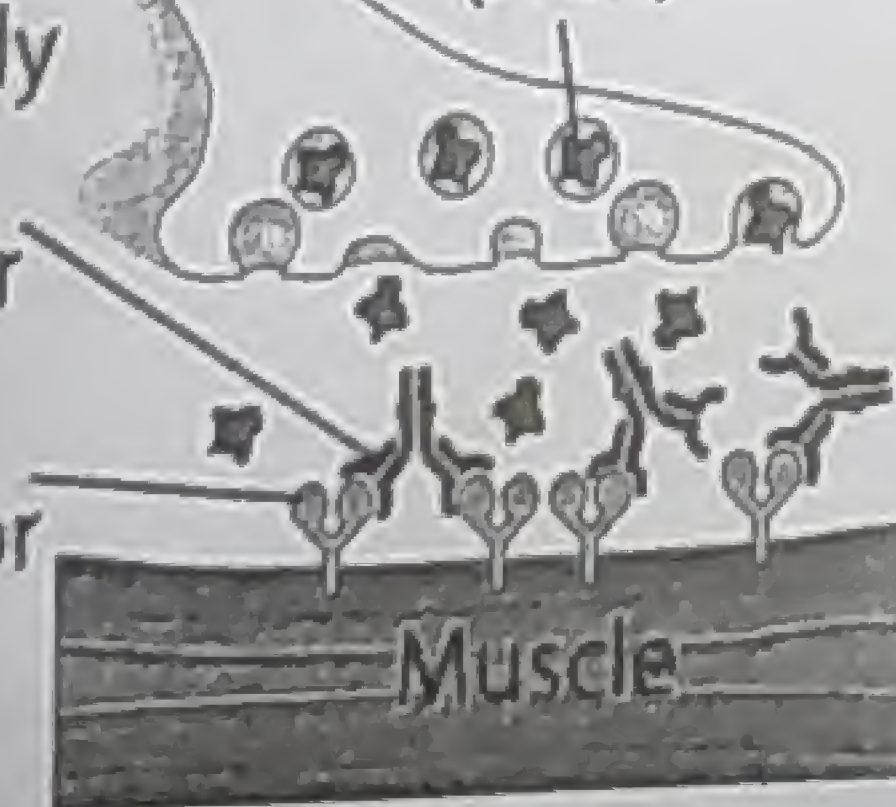
**Antibody stimulates receptor without ligand**

Nerve ending

Antibody to ACh receptor

ACh receptor

Acetylcholine (ACh)



**Antibody inhibits binding of ligand to receptor**

##### Good pasture's syndrome

IgG

binds glycoproteins

on lung &

glomerular cells

Destruction



Goodpasture syndrome

#### Exogenous

Rheumatic fever

Hyperacute graft rejection

**Antistreptococcal IgG**

cross react with

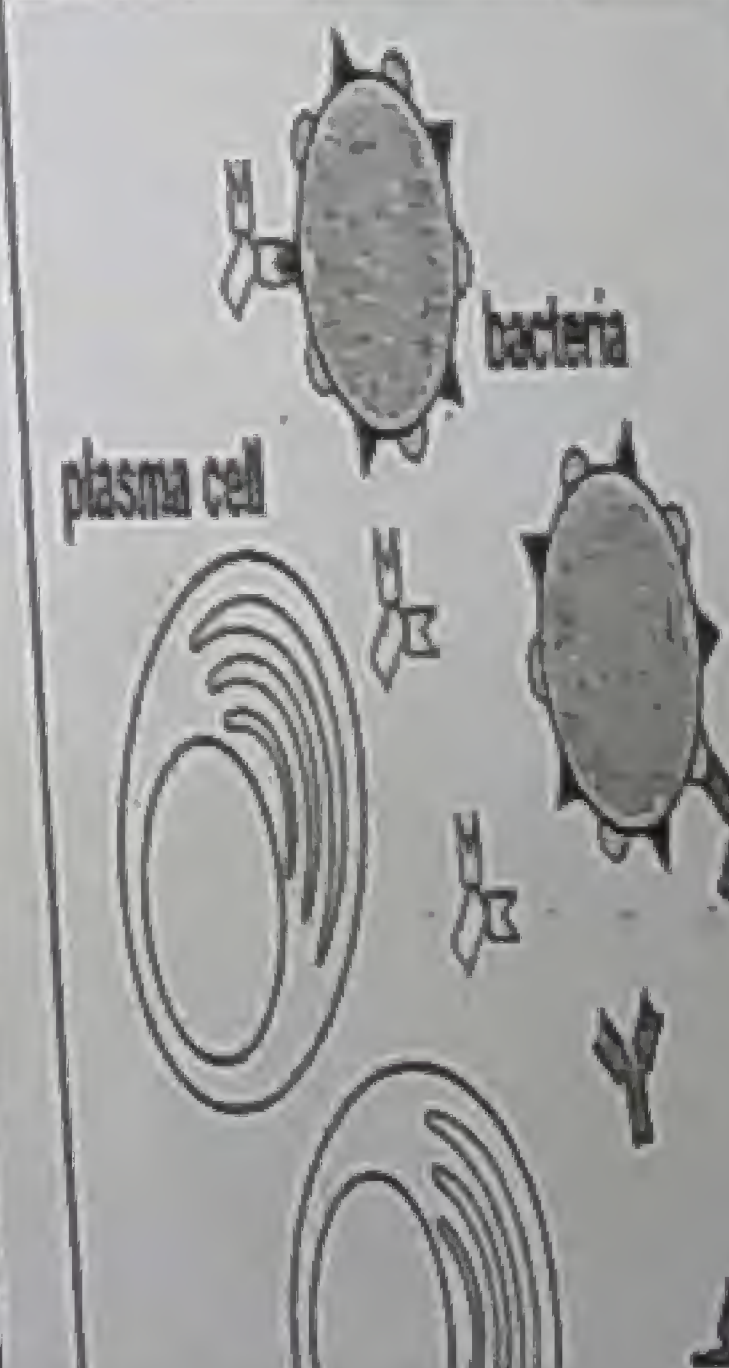
heterophil Ag

on heart muscle

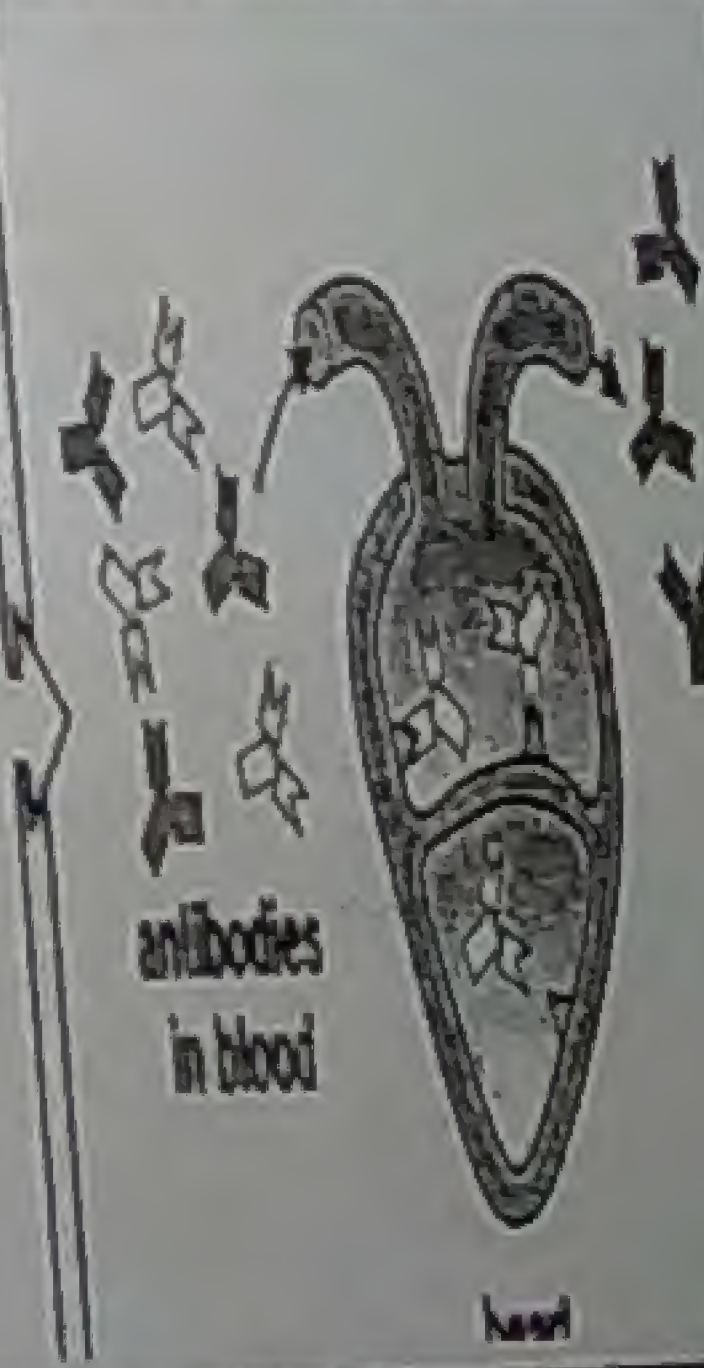
(molecular mimicry)



Streptococcal cell wall stimulates antibody response



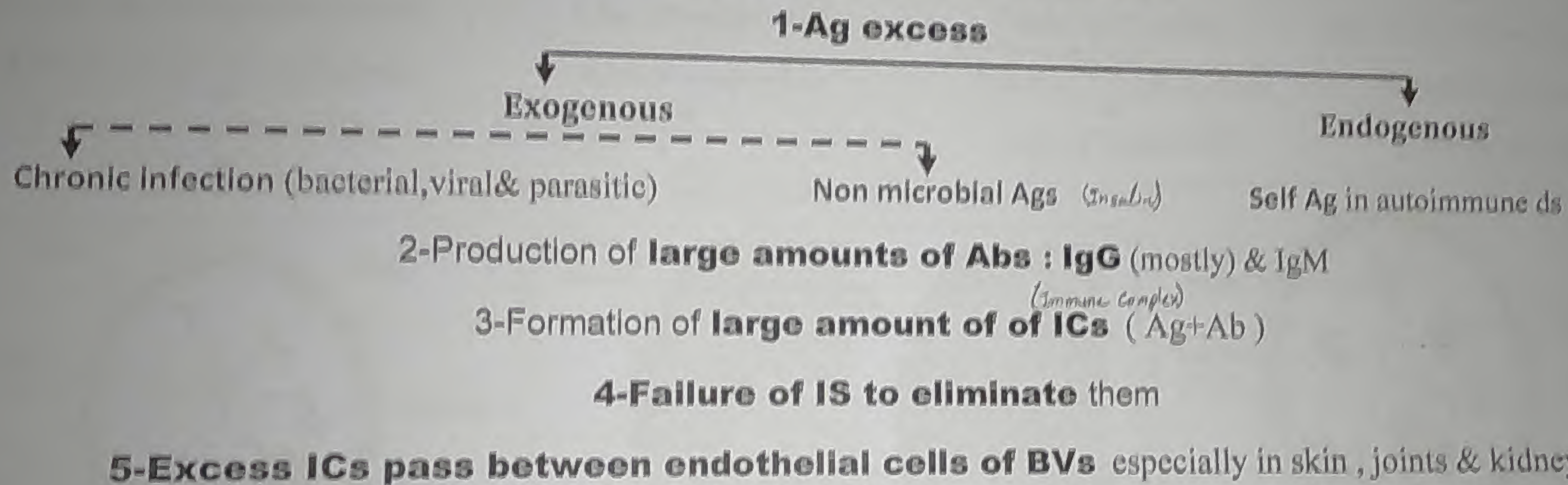
Some antibodies cross-react with heart tissue causing rheumatic fever





# Type III ( Immune complex ) Hypersensitivity

## Etiology & Mechanism



Type 3 - immune complex hypersensitivity

Figure 3a

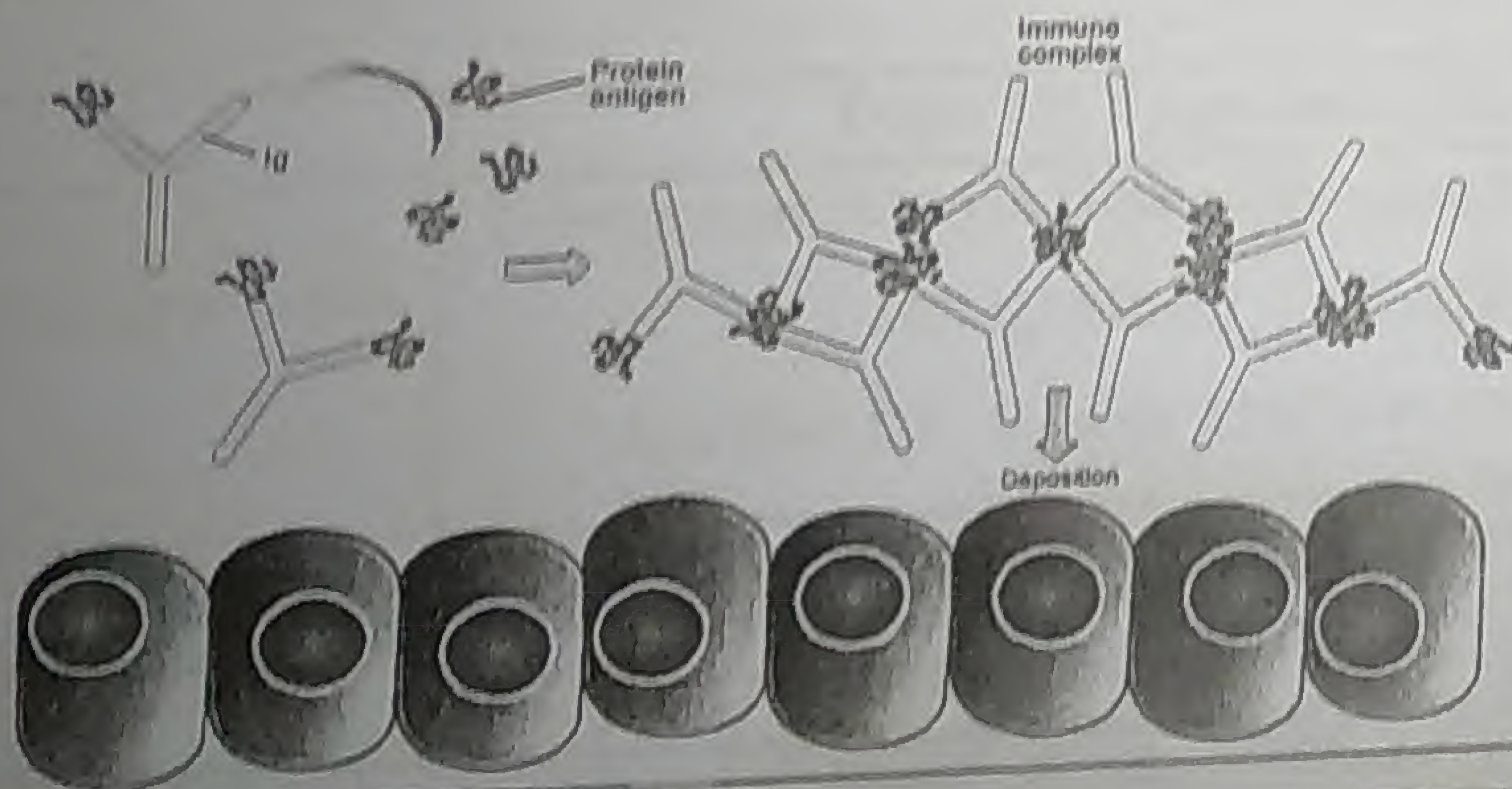
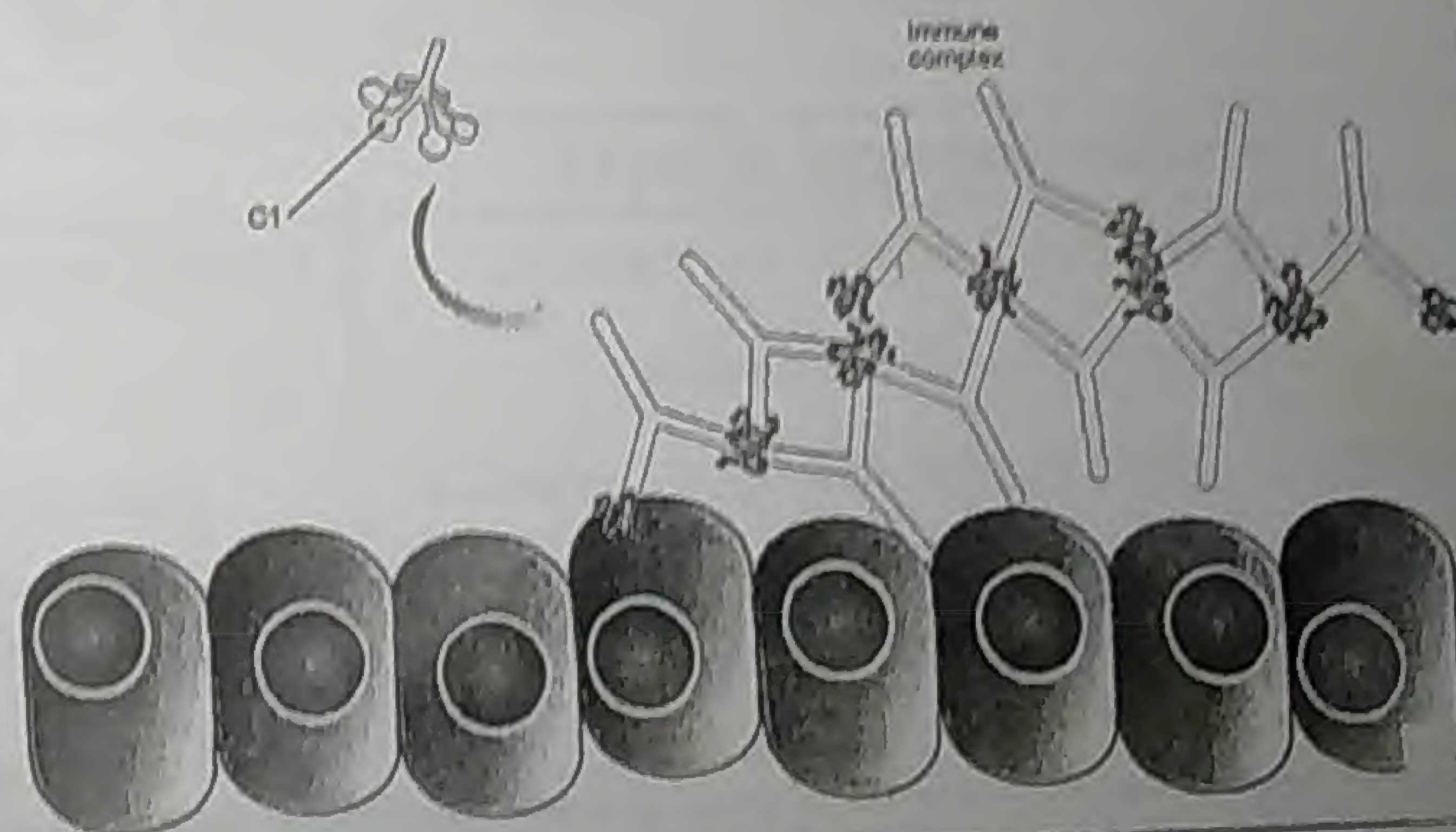
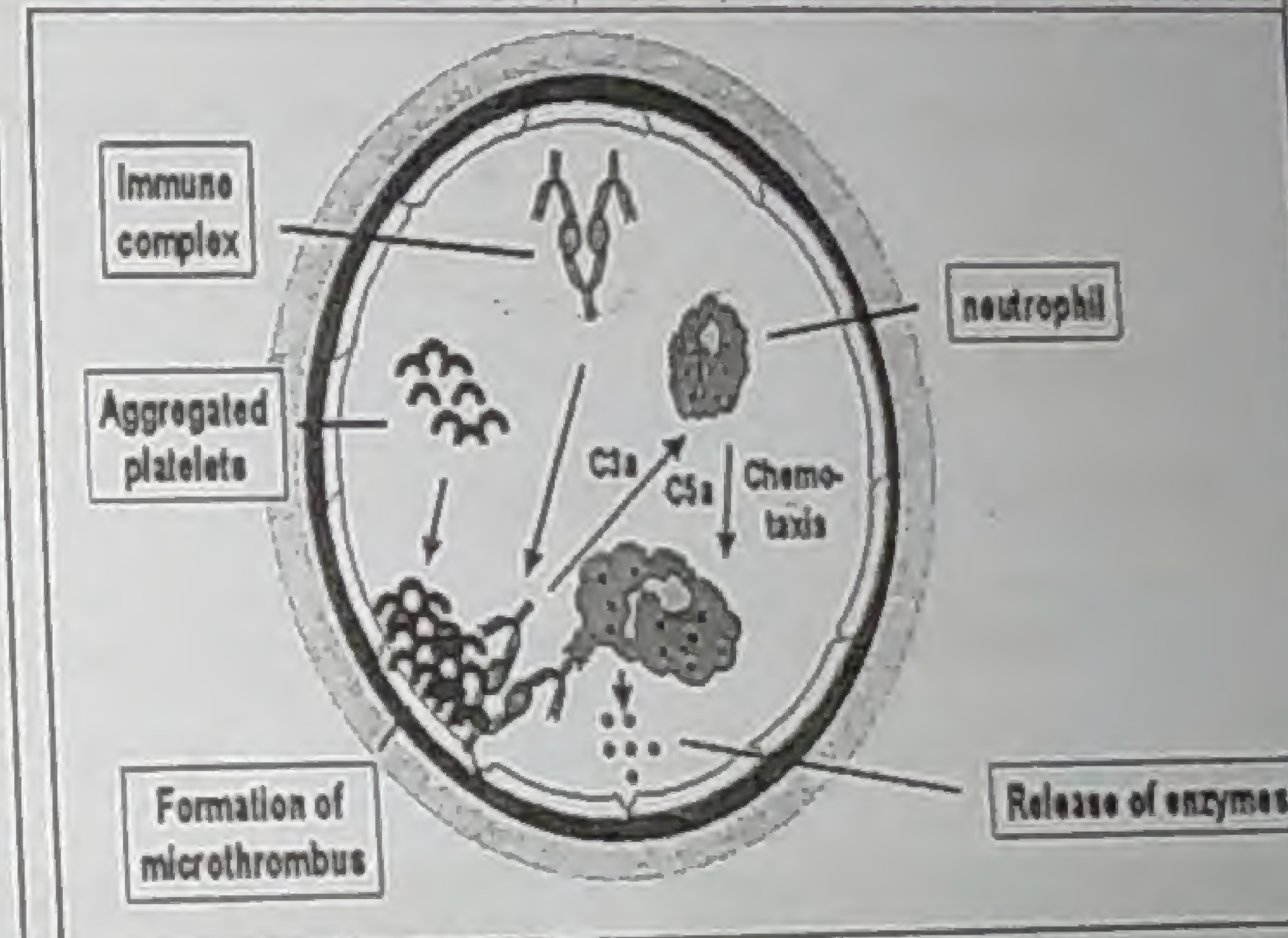
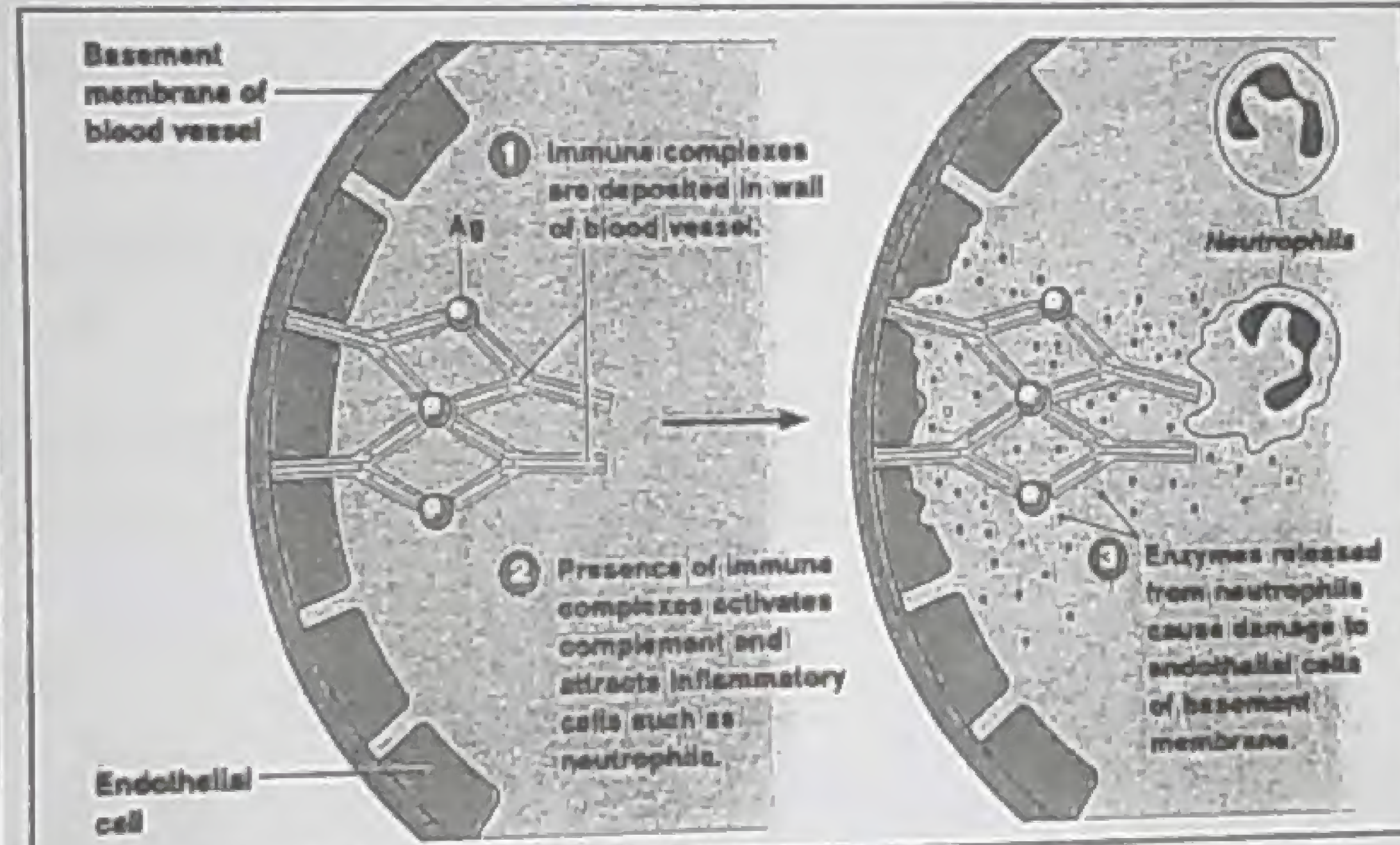
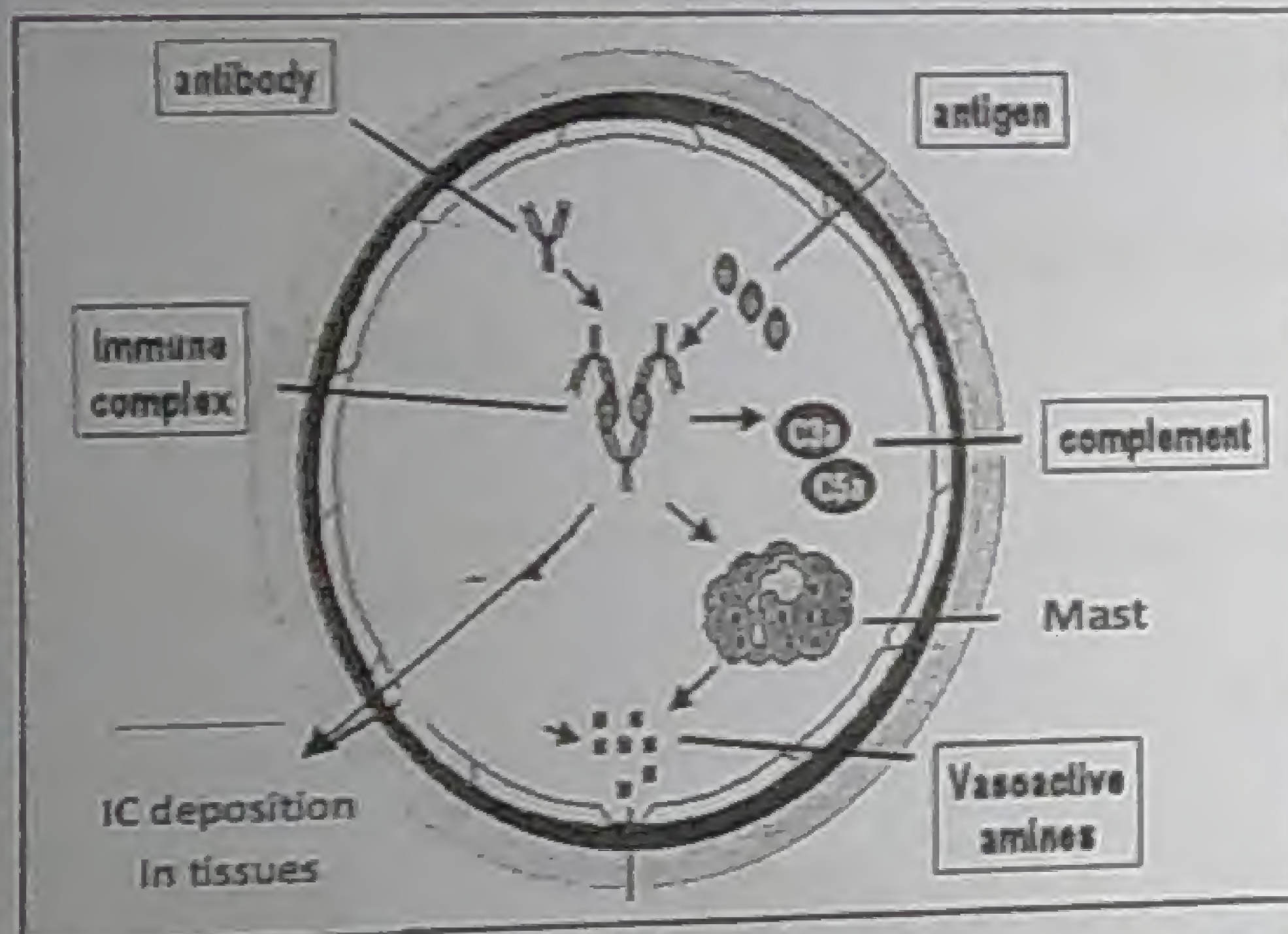
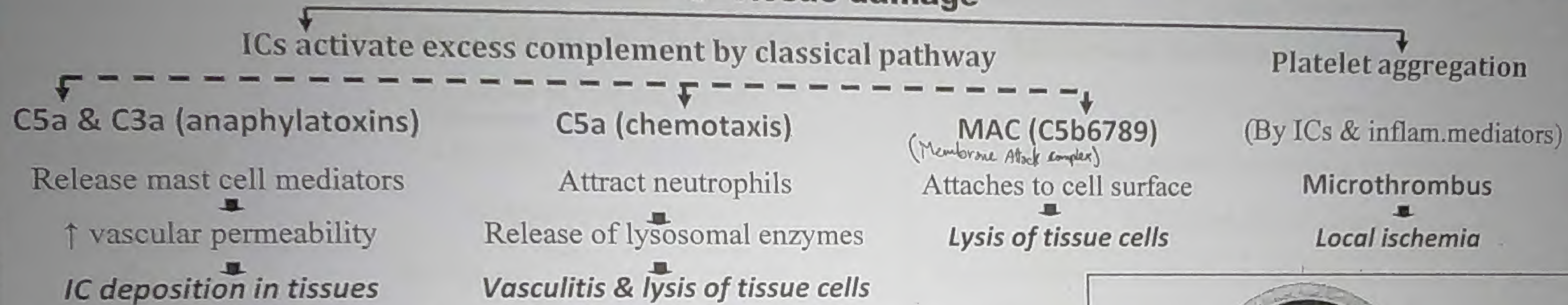


Figure 3b





## 6 -Tissue damage



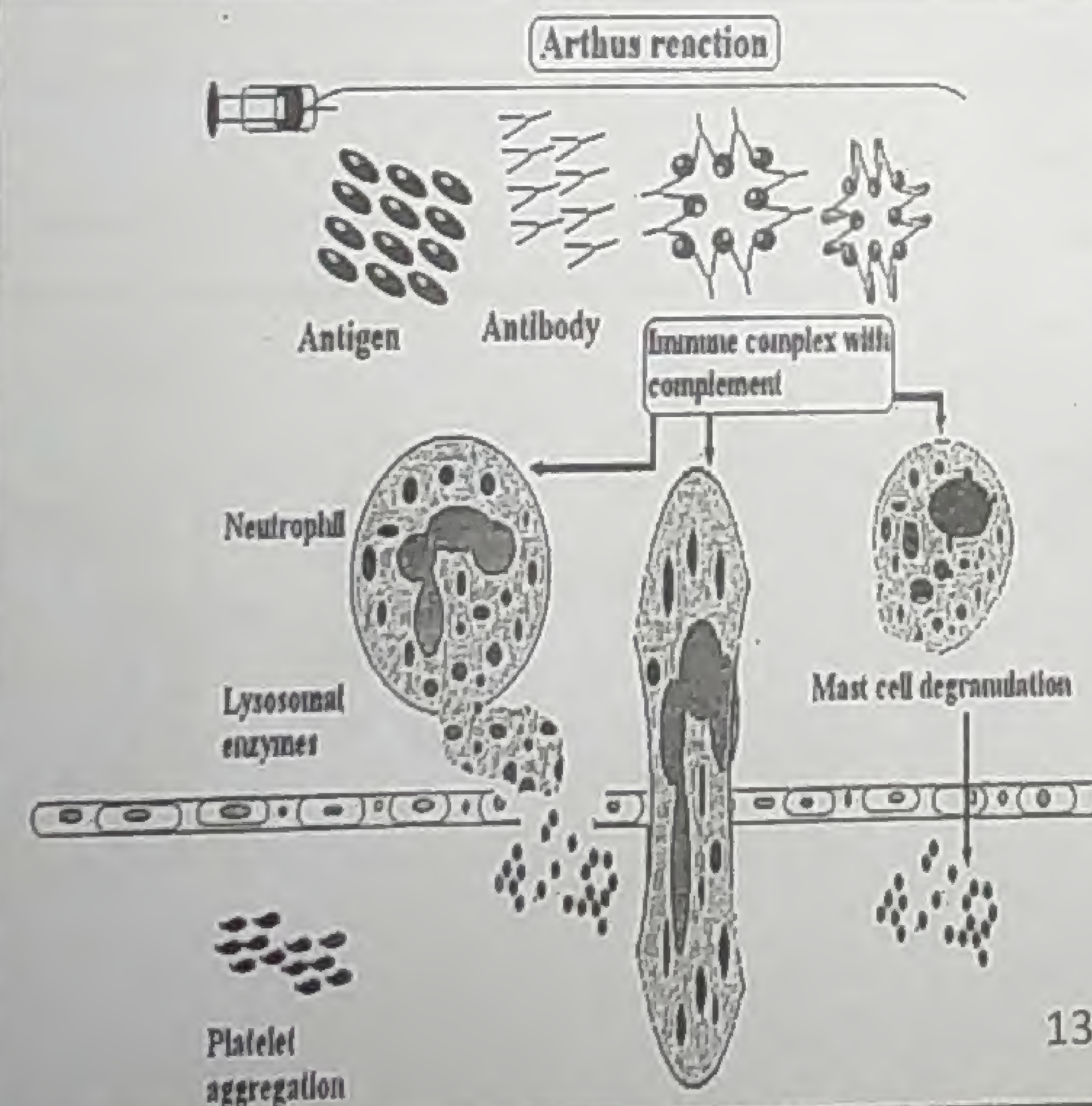
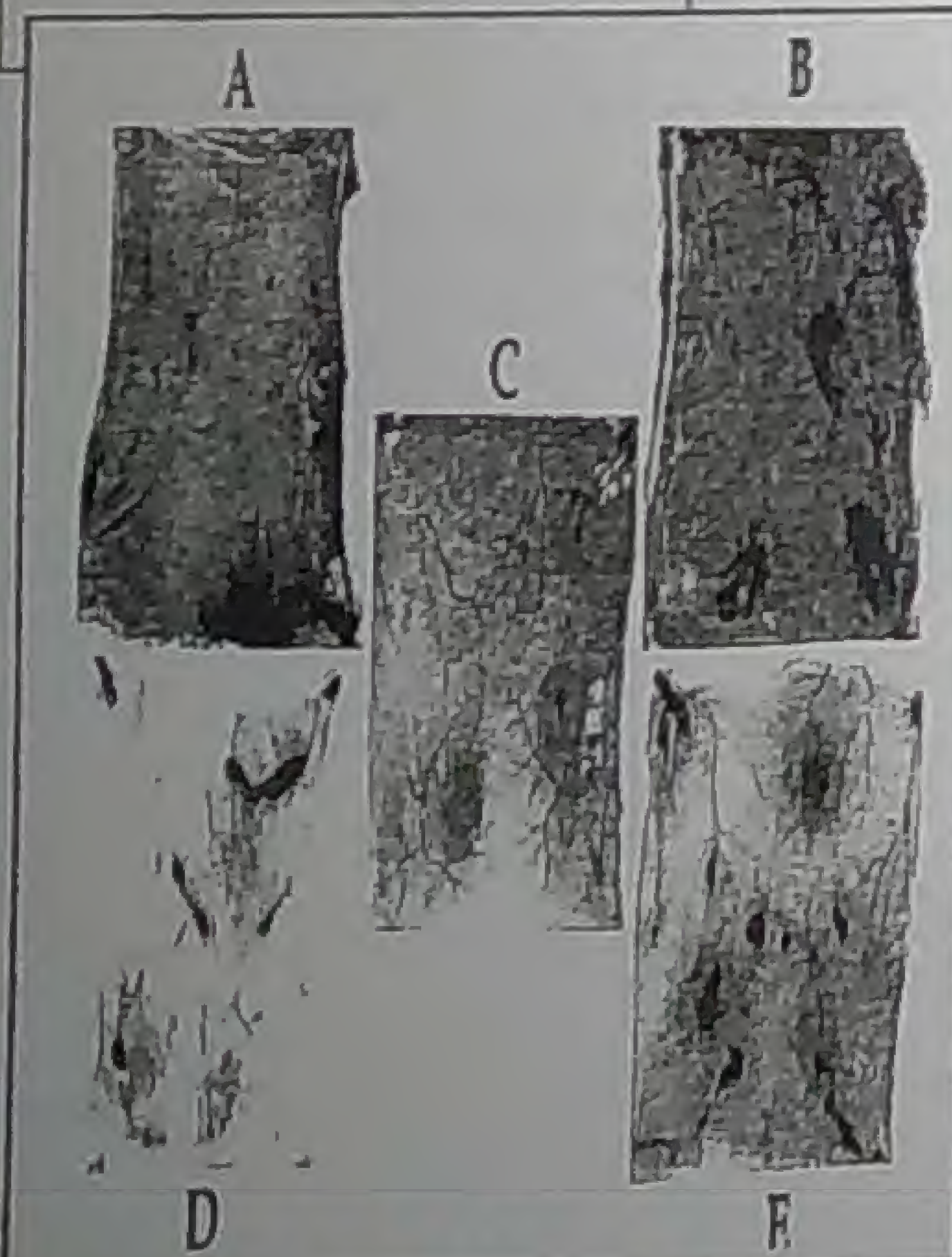
	Type III hypersensitivity	Type II hypersensitivity
<b>Diagnosis</b>	1-Detection of ICs in tissues by using Fluorescein labeled i. Anti IgM & IgG    ii. Anti C3b 2- ↓ free C3 : By single radial immunodiffusion	1-Detection of Abs & complement in lesions biopsy : by IF 2-Detection of free Abs in tissue : by ELISA
<b>Treatment</b>	1-Corticosteroids : ↓ inflammation 2-Plasmapheresis (in severe cases): ↓ circulating ICs ↳ Replacement of plasma containing IC by fresh frozen plasma.	1-Anti-inflammatory drugs 2-Immunosuppressive drugs



# Clinical presentations

More Common than Type I

	I Arthus reaction ( localized )	II Serum sickness ( systemic )
1-Etiology	Repeated SC injection of: i. Insulin ii. Penicillin iii. Rabies vaccines المرض الكلي	Injection of foreign serum: (IV) i. Animal serum (containing antitoxins) ii. Plasma transfusion (Albumine)
2-Mechanisms & lesions	ID Ags can't diffuse out rapidly ↓ Bind to circulating Abs ↓ Local IC deposition in small arteries ↓ Local cutaneous vasculitis & necrosis	Excess Abs are formed against foreign serum proteins ↓ Widespread IC deposition in small arteries ↓ Vasculitis in ↓ Skin ↓ Joints ↓ Kidneys Rash arthritis Nephritis
3-Onset		Symptoms appear 1w after 1 <sup>st</sup> injection More rapidly with each repeated injection





## III-Other clinical syndromes

### Exogenous Ags

Chronic microbial ds

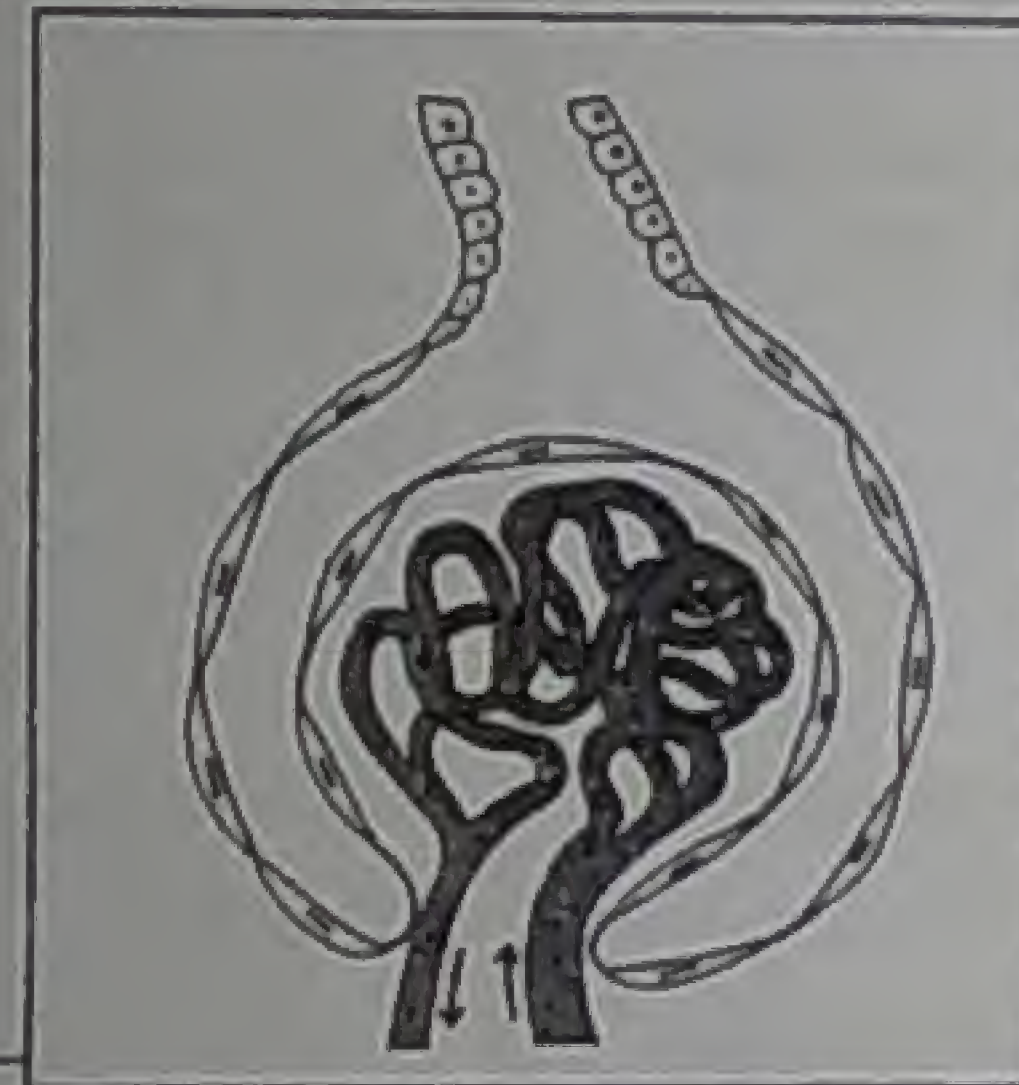
complicated by IC formation

Bacterial

Viral

Post-streptococcal  
glomerulonephritis

Hepatitis  
viruses



Farmer's lung  
(Ext.allergic alveolitis)

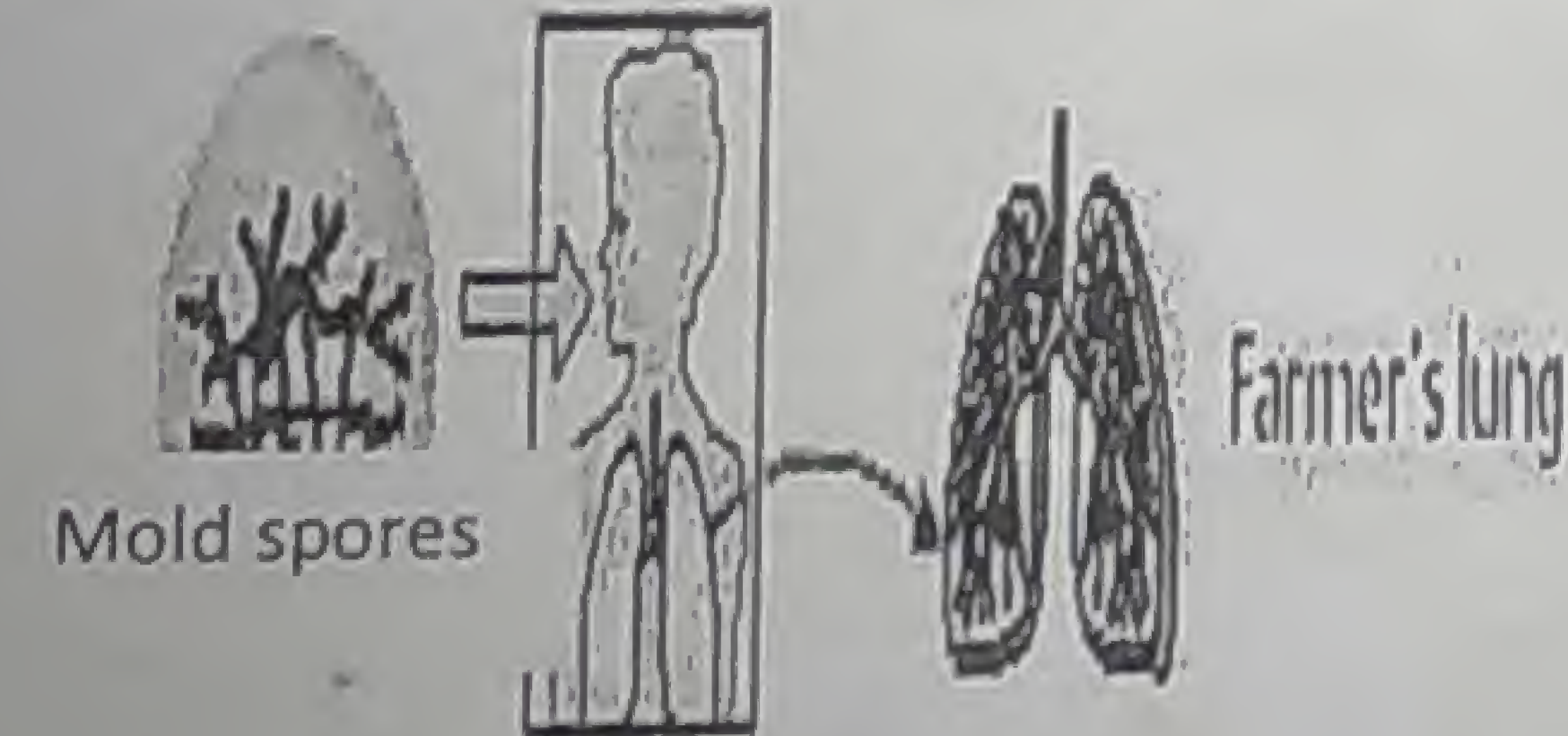
IgG against

→ mold spores &

→ pigeon feces

↓  
IC deposition

in lungs

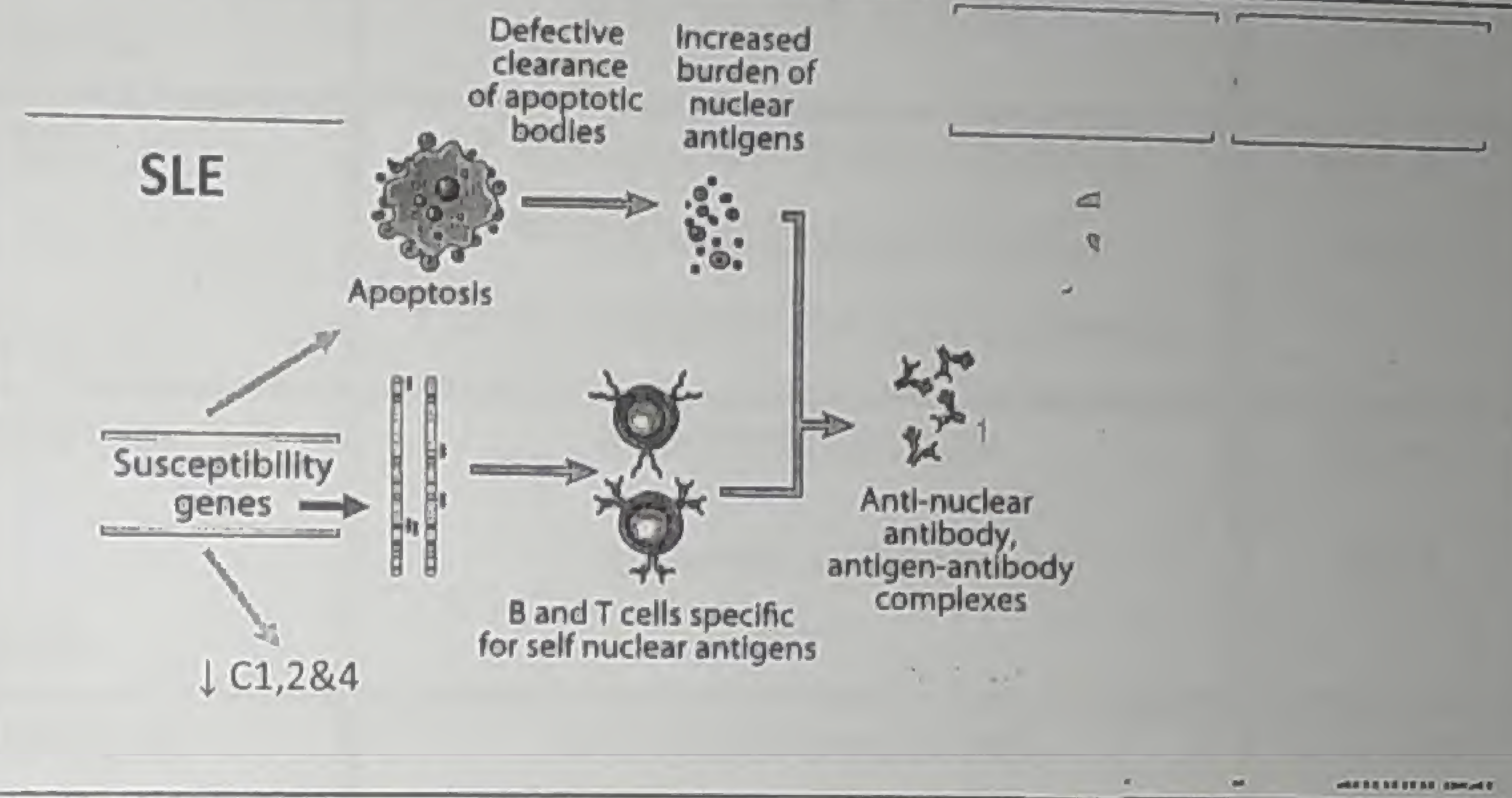


### Endogenous Ags

Auto Abs against self Ags

#### ◆SLE

#### ◆Rheumatoid arthritis



#### Rheumatoid arthritis

Susceptibility genes (HLA, other)

Failure of tolerance, unregulated lymphocyte activation

Antibodies

to self IgG

T and B cell responses to self antigens (including antigens in joint tissues)

Th1 cell

Lymphocytes, antibodies, and immune complexes enter joint

Joint

Synovial membrane

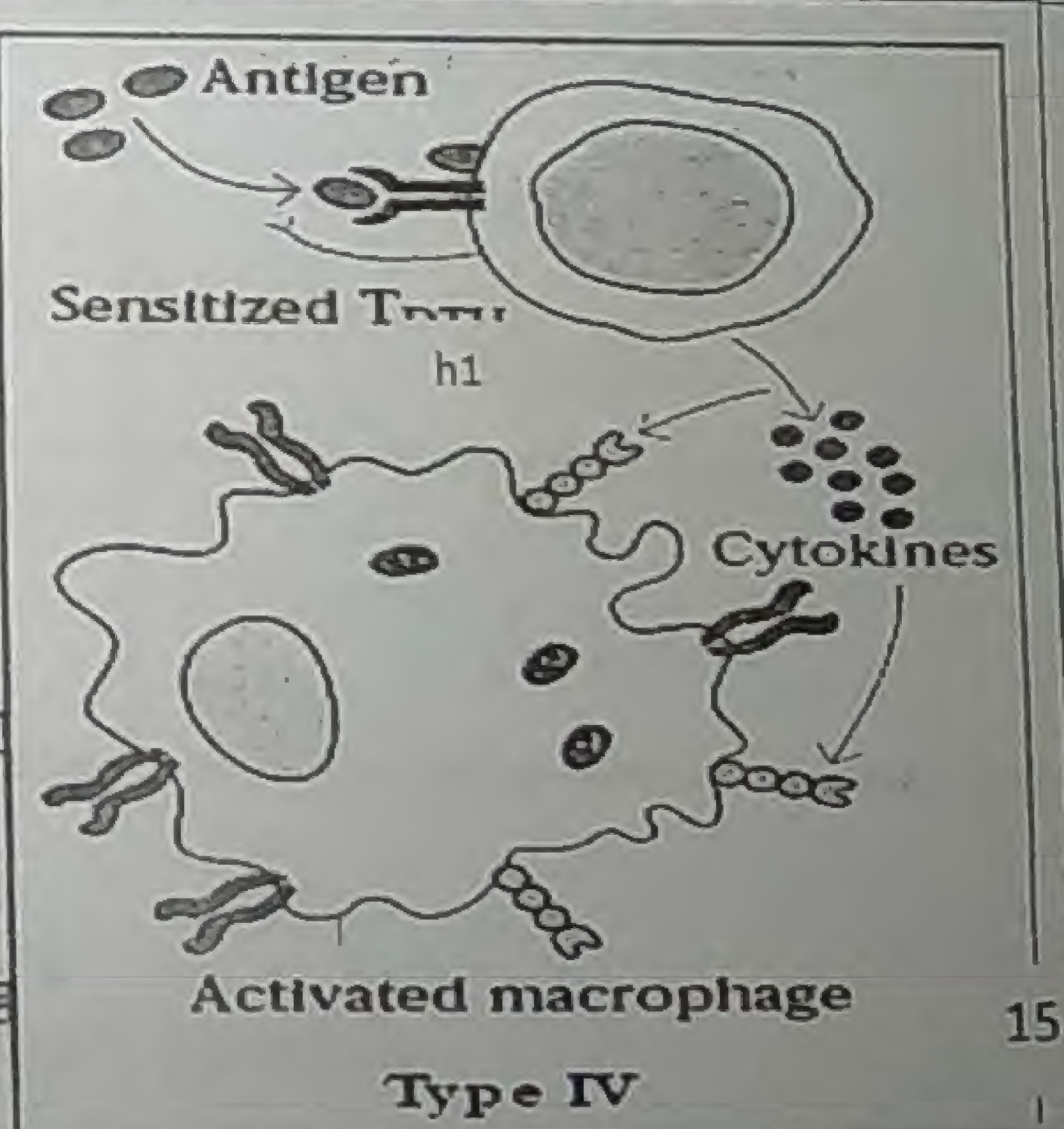
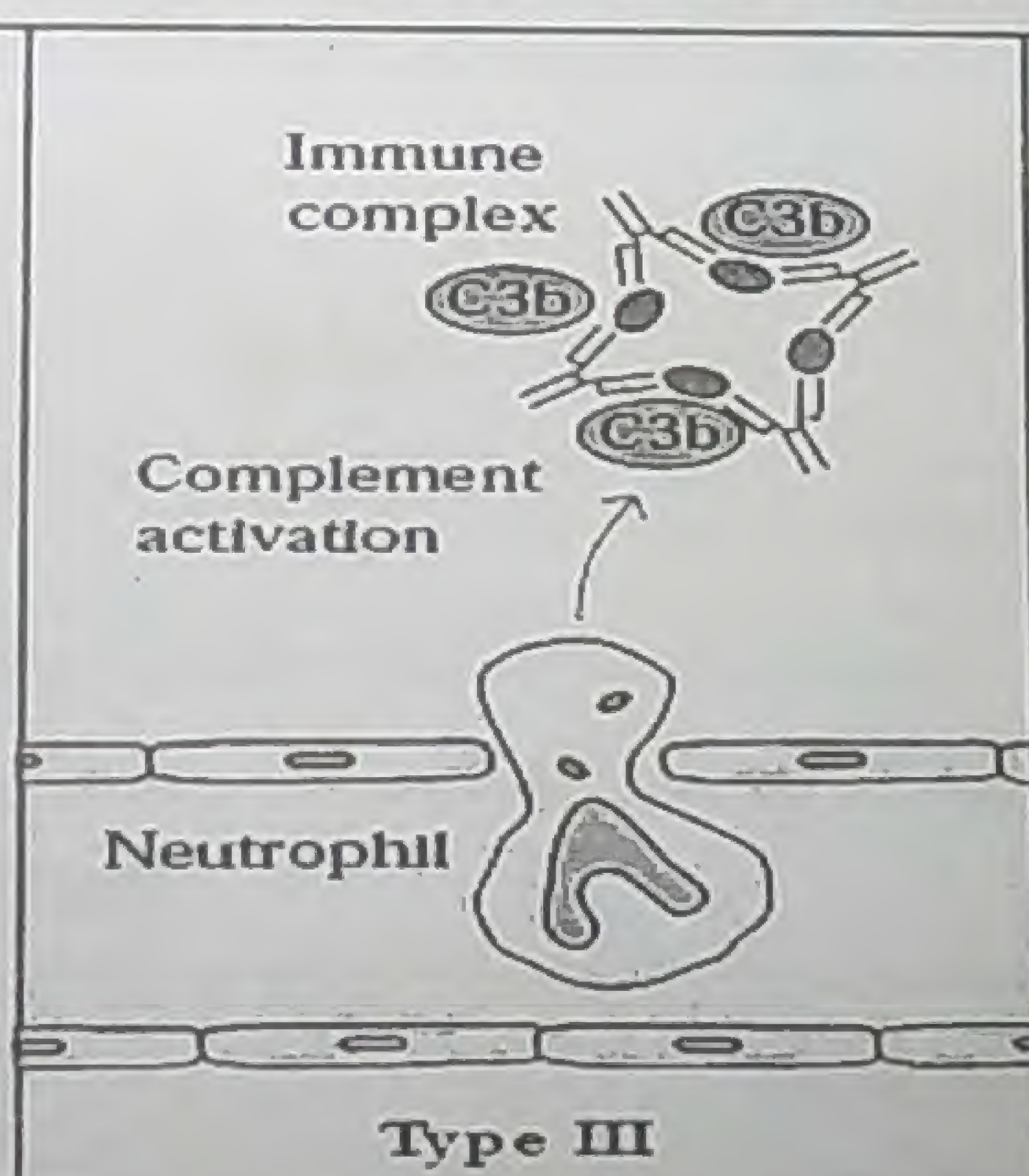
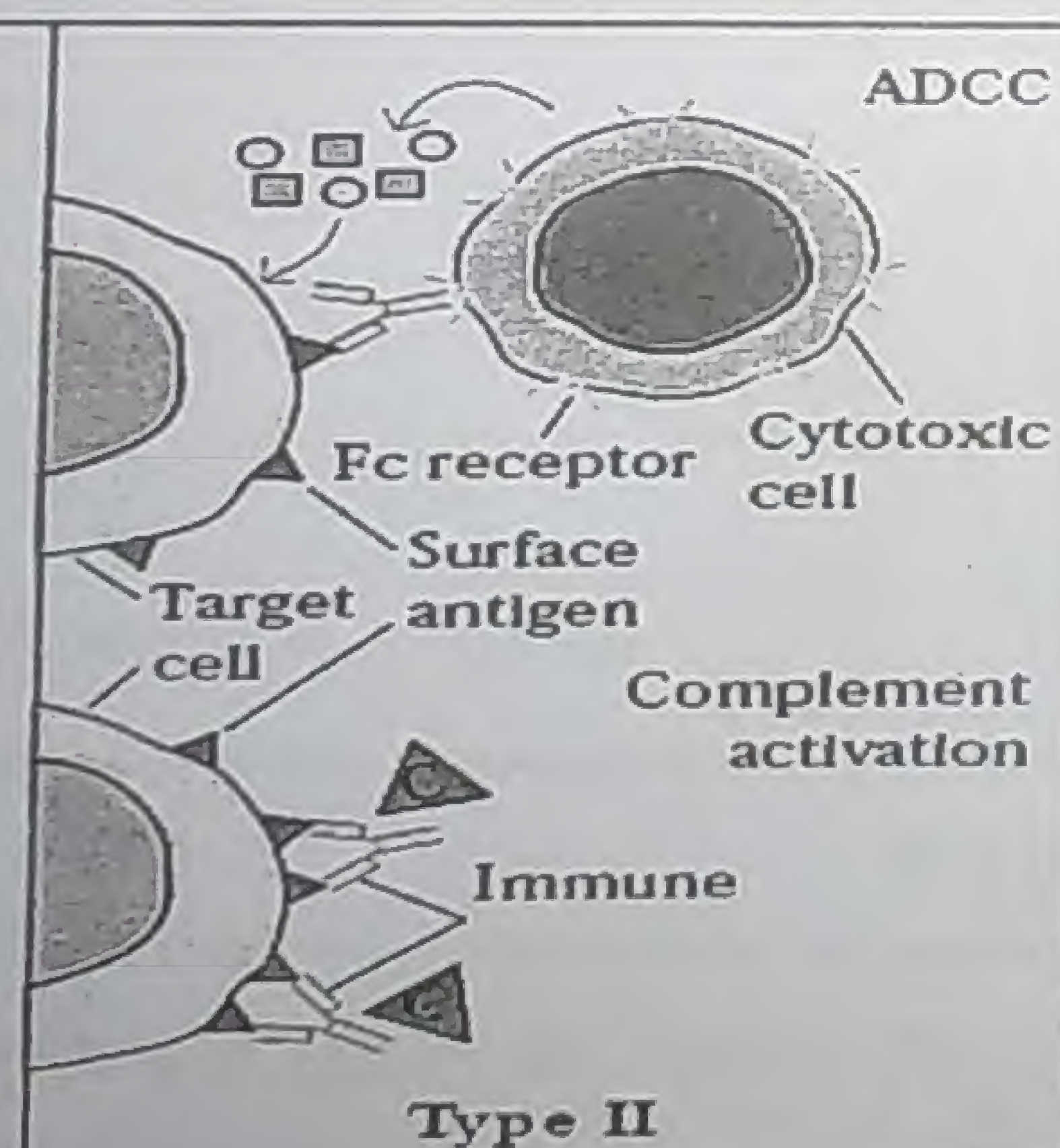
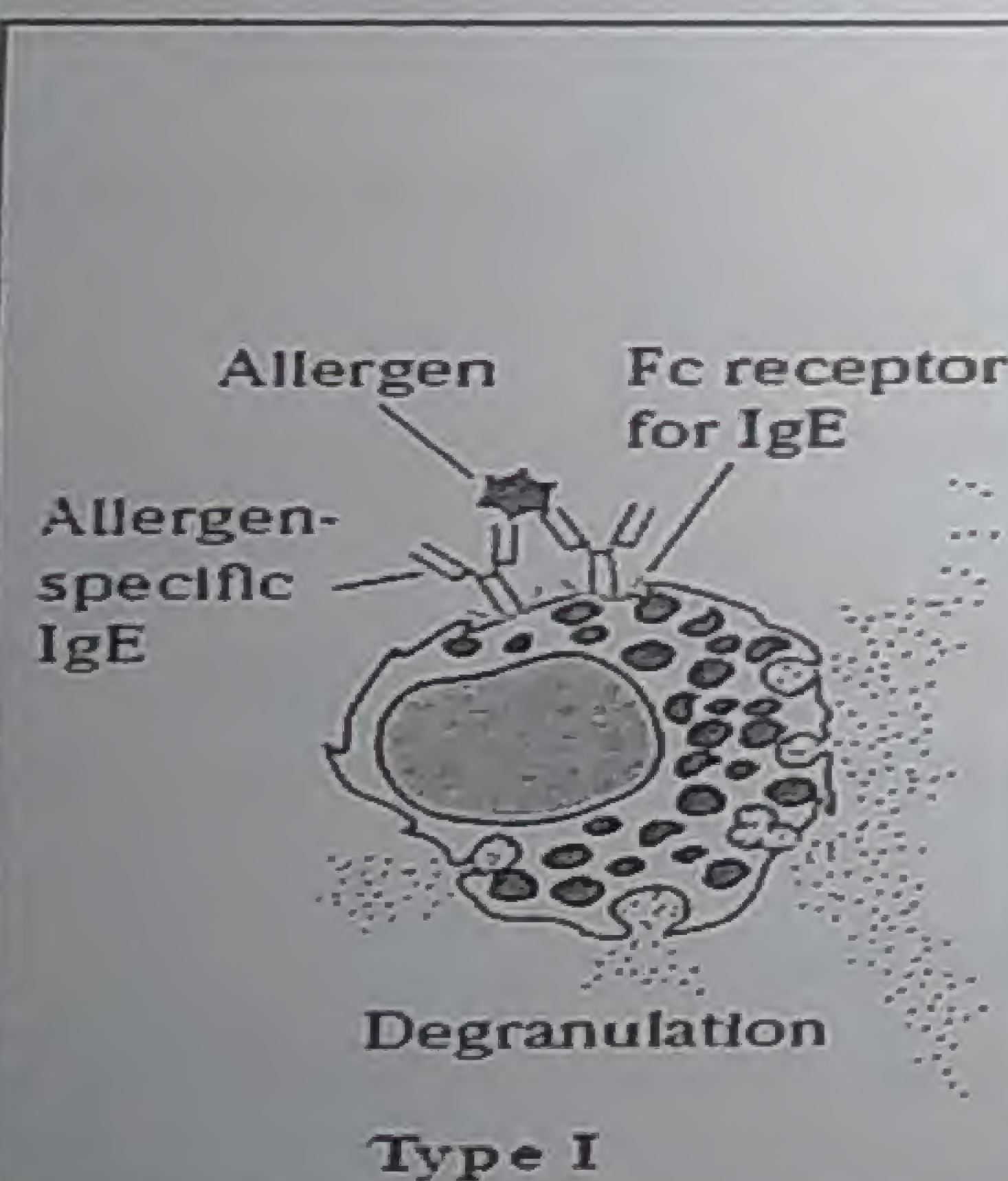
-Synovocyte activation  
-Cytokine production  
-Inflammation

Destruction of cartilage and bone



# Comparison between different types of hypersensitivity

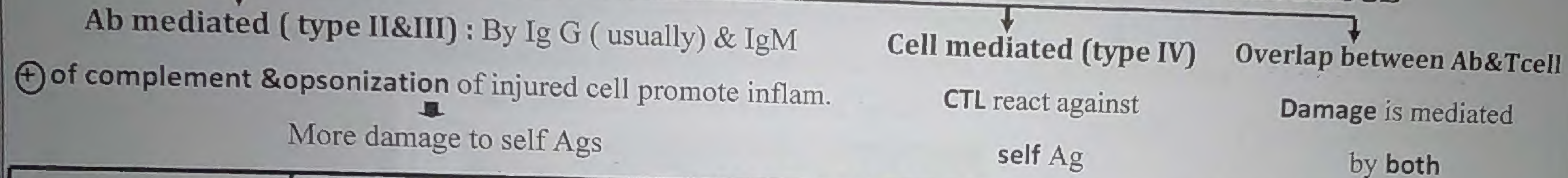
	Main factor	Pathogenesis	Examples	Time
<b>Type I</b>	IgE	Ag induces cross linking of <i>IgE bound to mast cells &amp; basophils</i> Release of vasoactive mediators	♣ Systemic anaphylaxis ♣ Bronchial asthma	Min to hrs
<b>Type II</b>	IgG & IgM	Ab against <i>cell surface Ags</i> Cell destruction by: Complement activation & ADCC	♥ Blood transfusion reaction ♥ Erythroblastosis fetalis ♥ Autoimmune hemolytic anemia	Hrs to days
<b>Type III</b>	ICs	Ag-Ab complexes <i>deposit in different tissues</i> ⊕ complement ↑↑ infiltration of neutrophils	♠ Arthus reaction ♠ Serum sickness	Hrs to days
<b>Type IV</b>	Cell mediated	<i>Sensitized Th1 release cytokines</i> ⊕ MQ or Tc	♦ Contact dermatitis ♦ Tuberculous lesions	2-4 days





# Autoimmune diseases

## Mechanisms of tissue damage in autoimmune diseases



	Disease	Target Ag	Clinical finding
<b>A- Type II hypersensitivity</b>	1-AI hemolytic anemia	<i>RBC</i> membrane protein	Anemia
	2- Rheumatic fever	<i>Myocardial</i> Ag	Myocarditis
	3-Good pasture's syndrome	Protein in BM of <i>glomeruli &amp; alveoli</i>	Nephritis & lung hge
	4-Myasthenia gravis	<i>Acetyl choline receptors</i> on muscle	Muscle weakness
	5-Grave's disease	<i>TSH receptor</i> on thyroid	Hyperthyroidism
<b>B-Type III hypersensitivity</b>	1-SLE	DNA & nucleoproteins	Nephritis, vasculitis, arthritis.
	2-Rheumatoid arthritis	Ab (anti Ig Ab are produced in joints)	Arthritis
	3-Poststrept. glomerulonephritis	Glomerular BM	Nephritis
<b>C-Type IV hypersensitivity</b>	1-Type I DM	Ags on <i>Langerhans cells</i> of pancreas	Diabetes
	2-Rheumatoid arthritis	Ag on the wall of <i>synovium</i>	Arthritis

## Types

Organ specific : Myasthenia gravis & Grave's ds

Non organ specific : SLE



# Laboratory diagnosis

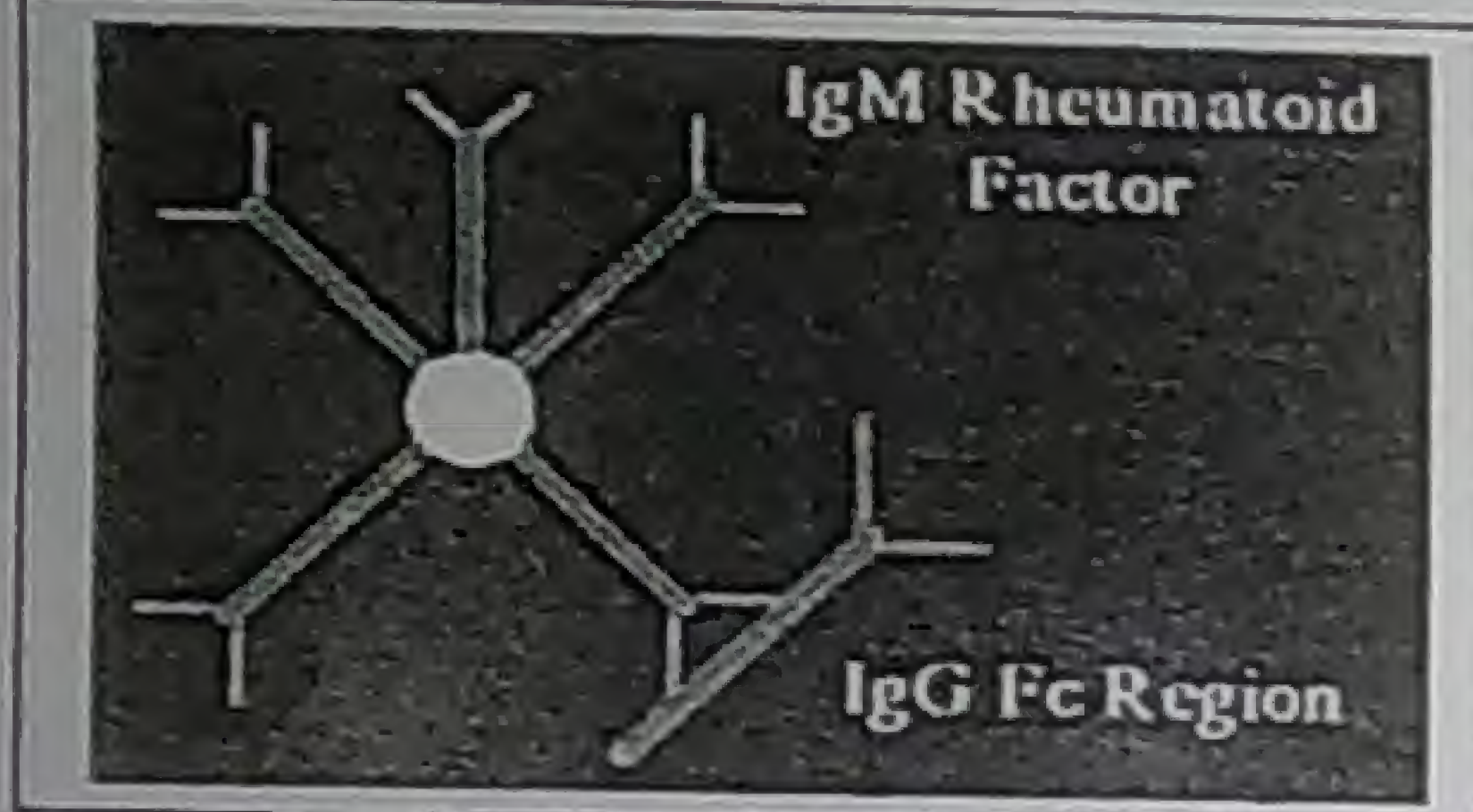
↑ serum Igs  
↓ complement levels

Detection of specific autoAbs in serum

Detection of ICs

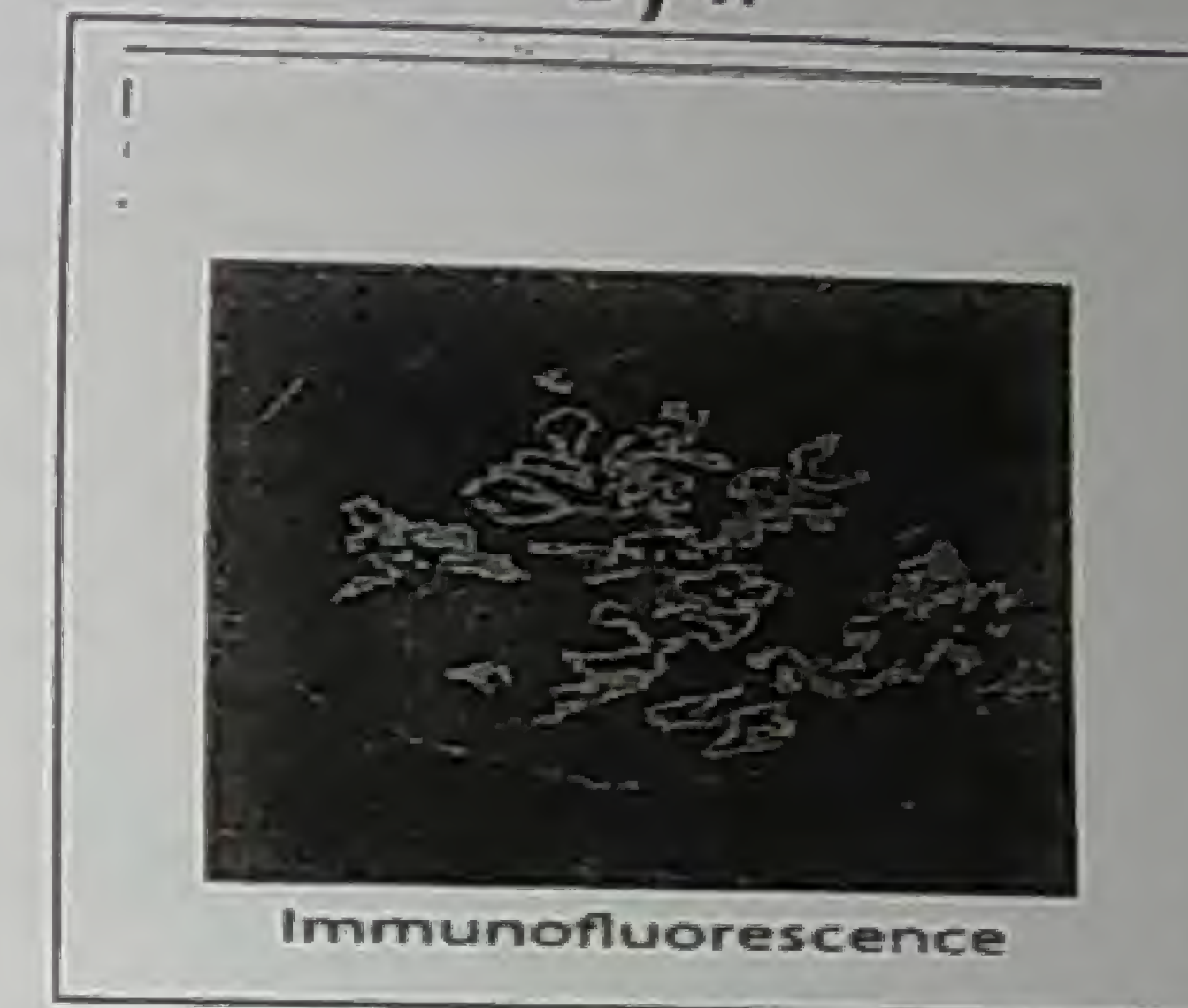
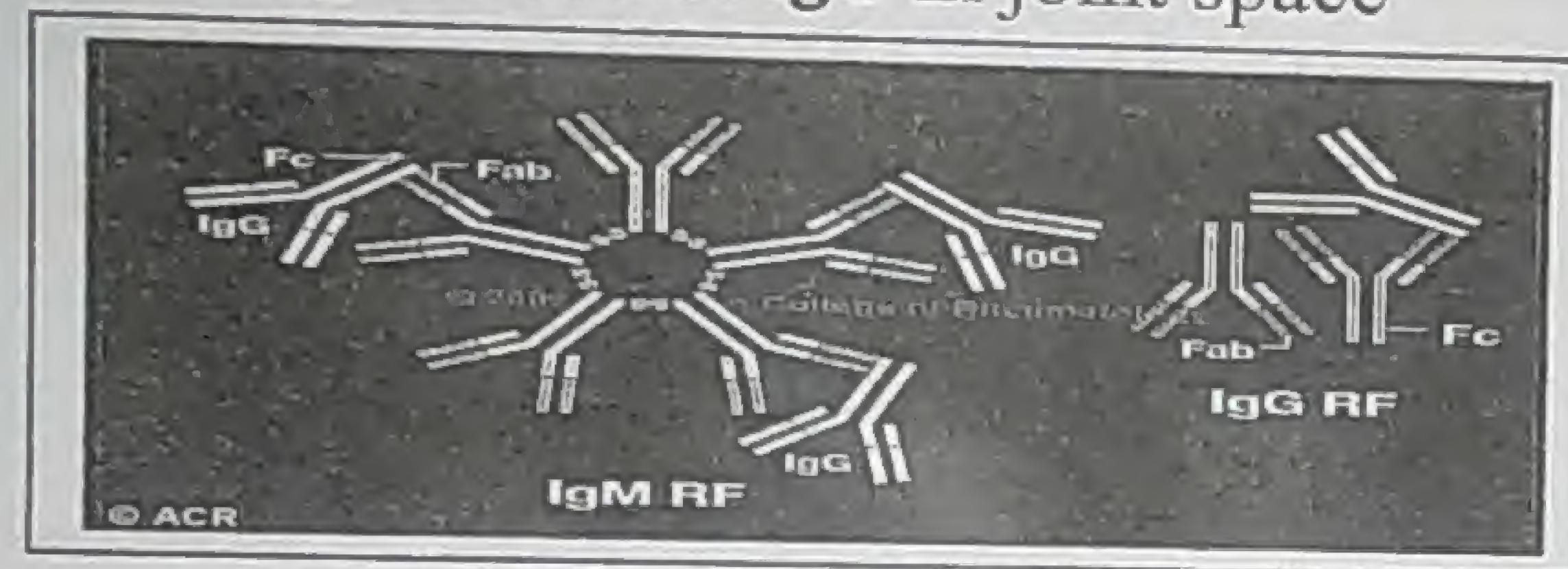
in serum & tissues

By IF



*Rheumatoid factor* in rheumatoid arthritis  
Abs against Fc of IgG in joint space

*Antinuclear Abs*  
in SLE



## Treatment

### I-RAP

Replacement & symptomatic therapy

Antagonists of proinflam.cytokines

Plasmapheresis

*Anti-thyroid drugs*

*Insulin*

*NSAIDs*

*Monoclonal Abs: Anti-TNFα*

*Remove offending*

in Grave's ds

in type I DM

in rheumatoid arth.

in rheumatoid arthritis

*ICs or Abs*

### II-Immunosuppressive drugs

⊖ cytokines secretion

⊖ T cell activation by ⊖ costimulation

Block T cell proliferation

⊖ *MQ cytokines*

⊖ *T cell cytokine: IL2*

*Soluble CTLA-4*

*Methotrexate*

Corticosteroids

Cyclosporine

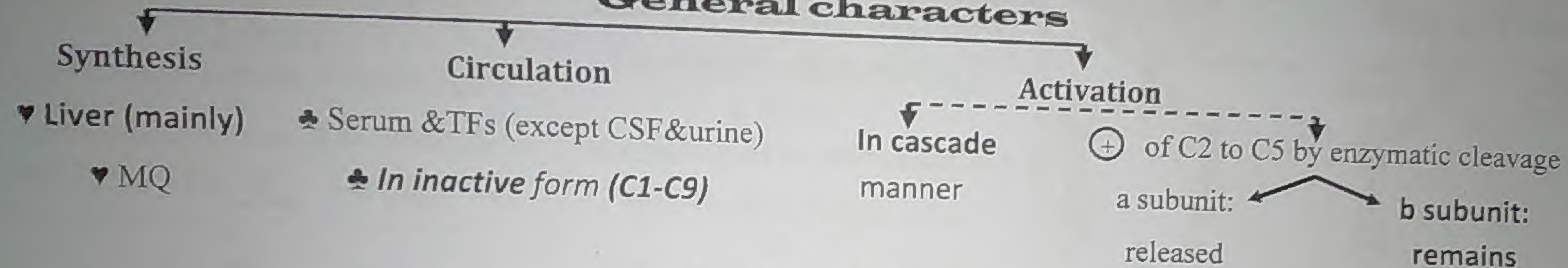
Bind B7 mol.

⊖ its binding to CD28

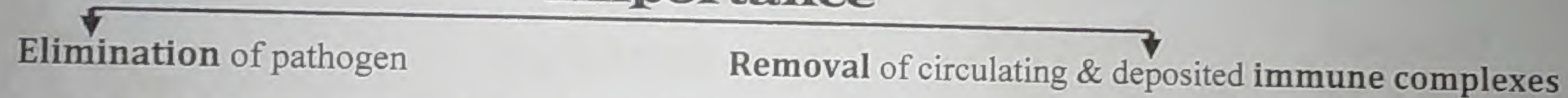


# Complement system

## General characters



## Importance



## Comparison between the 3 pathways of complement activation

	Classical pathway	Lectin pathway	Alternative pathway
1-Activated by	Ag-Ab complex ( <i>Adaptive</i> immunity)	Mannose on pathogen surface ( <i>Innate</i> immunity)	Pathogen surface
2-1 <sup>st</sup> complement ⊕	C1	Mannose binding lectin (P.P)	C3b
3-C2 & C4	Activated		Not activated
4-C3 convertase	Same : <i>C4b2b</i>		<i>C3bBb</i>
5- C5 convertase	Same : <i>C4b2b3b</i>		<i>C3bBb3b</i>
6-Membrane attack complex (MAC)	<i>C5b6789</i> (common final pathway)		



## Classical pathway

## Lectin pathway

### 1-Initiation & 1<sup>st</sup> complement activated

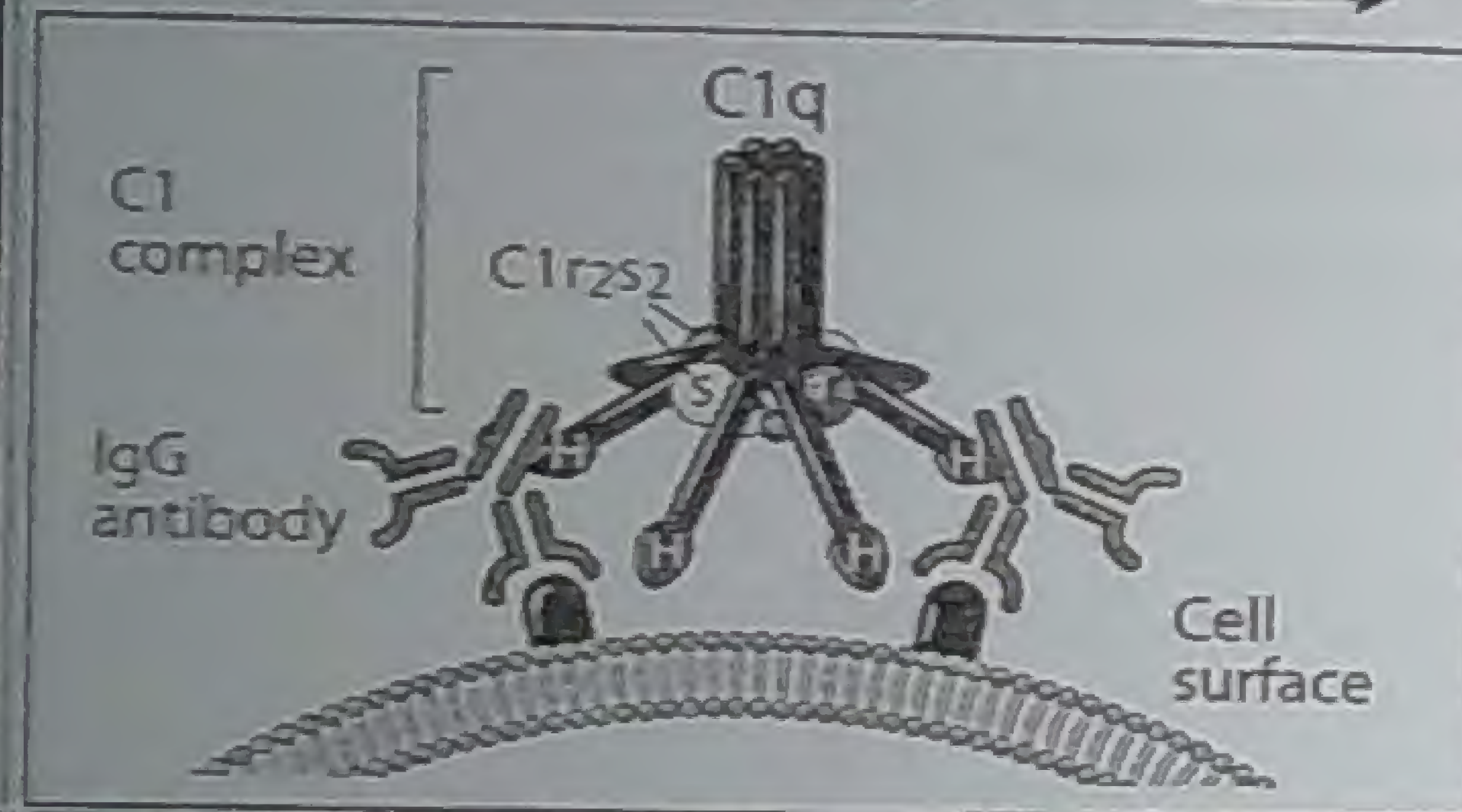
Ab :IgM (most efficient) or IgG3,1,2

↓ Binds

Microbial surface or other Ags

Conformational change of **Fc (CH2)** of Ab

→ ⊕ of C1q → ⊕ C1r → ⊕ C1s



Mannose binding lectin (MBL)

[ structurally similar to C1q ]

↓ Binds

Polysaccharide on microb.surface

(not found on human cells)

Conformational change of **MBL**

⊕ of **MASP1 & MASP2**

(man.bind.lect.assoc.protease)

[structurally similar to C1r & C1s]

### 2-Formation of C3 convertase

Activated C1 cleaves C4 & C2 into:

Activated MASP1&2 cleaves C4 & C2 into:

i. 2 small fragments **C4a & C2a** : *Released* into surrounding space

ii. 2 large fragments: **C4b&2b** → *bind* to bacterial CW → **C4b2b (C3 convertase)**

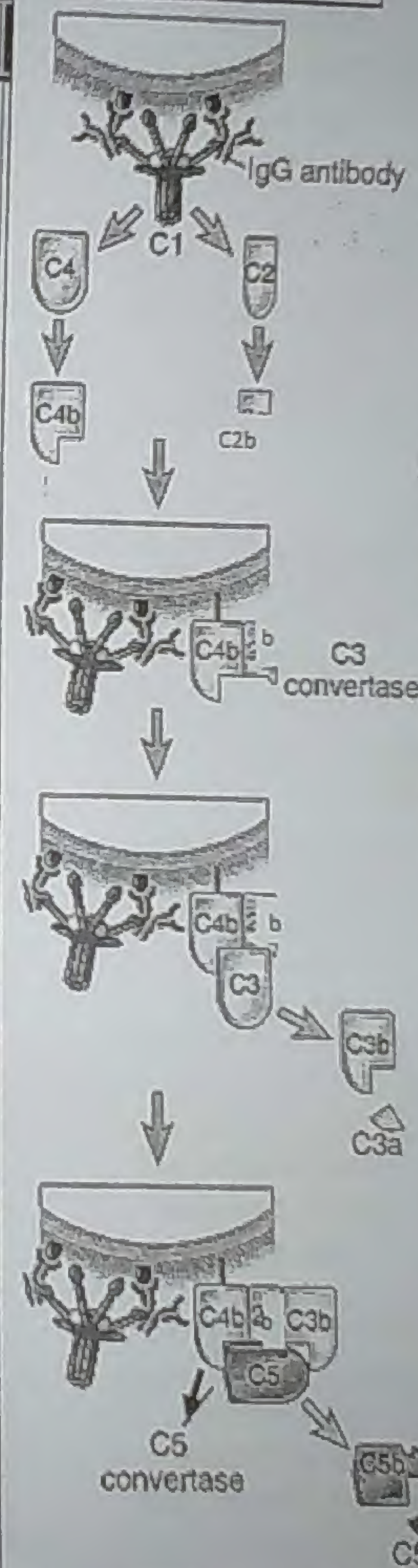
### 3-Formation of C5 convertase

C4b2b bind & cleave **C3** into:

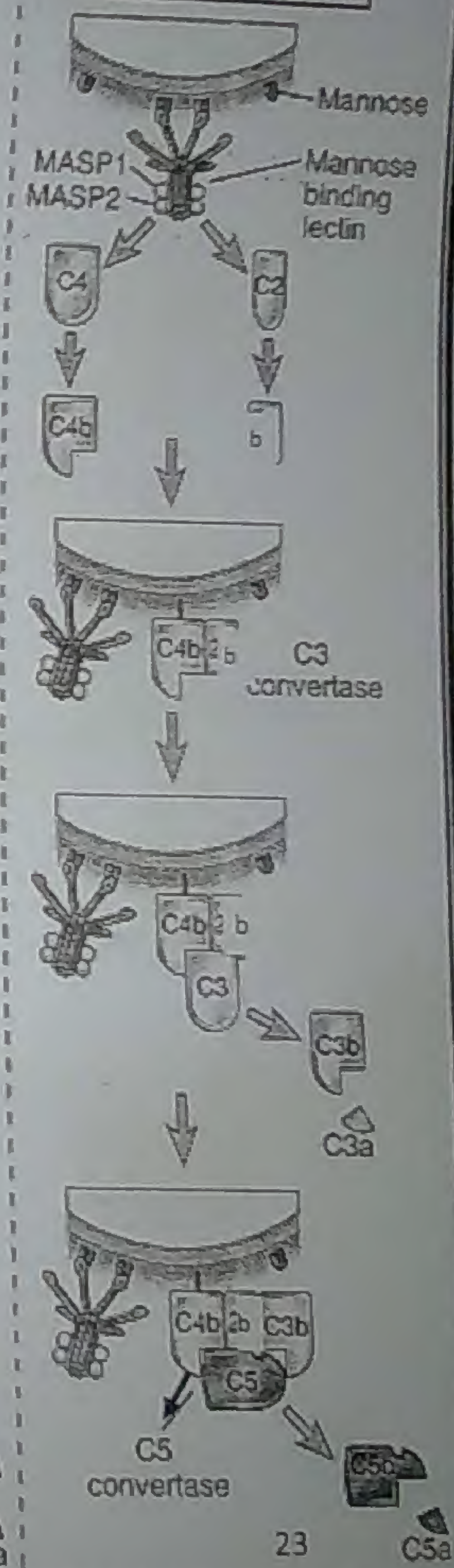
i. **C3a** : *released* into surrounding space

ii. **C3b** : *Reacts* with C4b2b → **C4b2b3b (C5 convertase)**

### Classical Pathway



### Lectin Pathway





## Alternative pathway

### 1-Initiation & 1<sup>st</sup> complement activated

*Spontaneous cleavage of C3 in plasma at low rate*

**C3b** (quickly hydrolysed if no microbe in circulation)

Binds **Microbial surface**

Conformational change of **C3b**

### 2-Formation of C3 convertase

*C3b binds to Factor B*

**C3bB**

*Factor D* cleaves factor B in the complex

**Ba**

**Bb**

(small & inactive → **released**)

(large & remains **attached**)

**C3bBb (C3 convertase)**

Stabilized by **properdin** (Prolongs its action)

### 3-Formation of C5 convertase

*C3bBb bind & cleave additional C3*

**C3a**

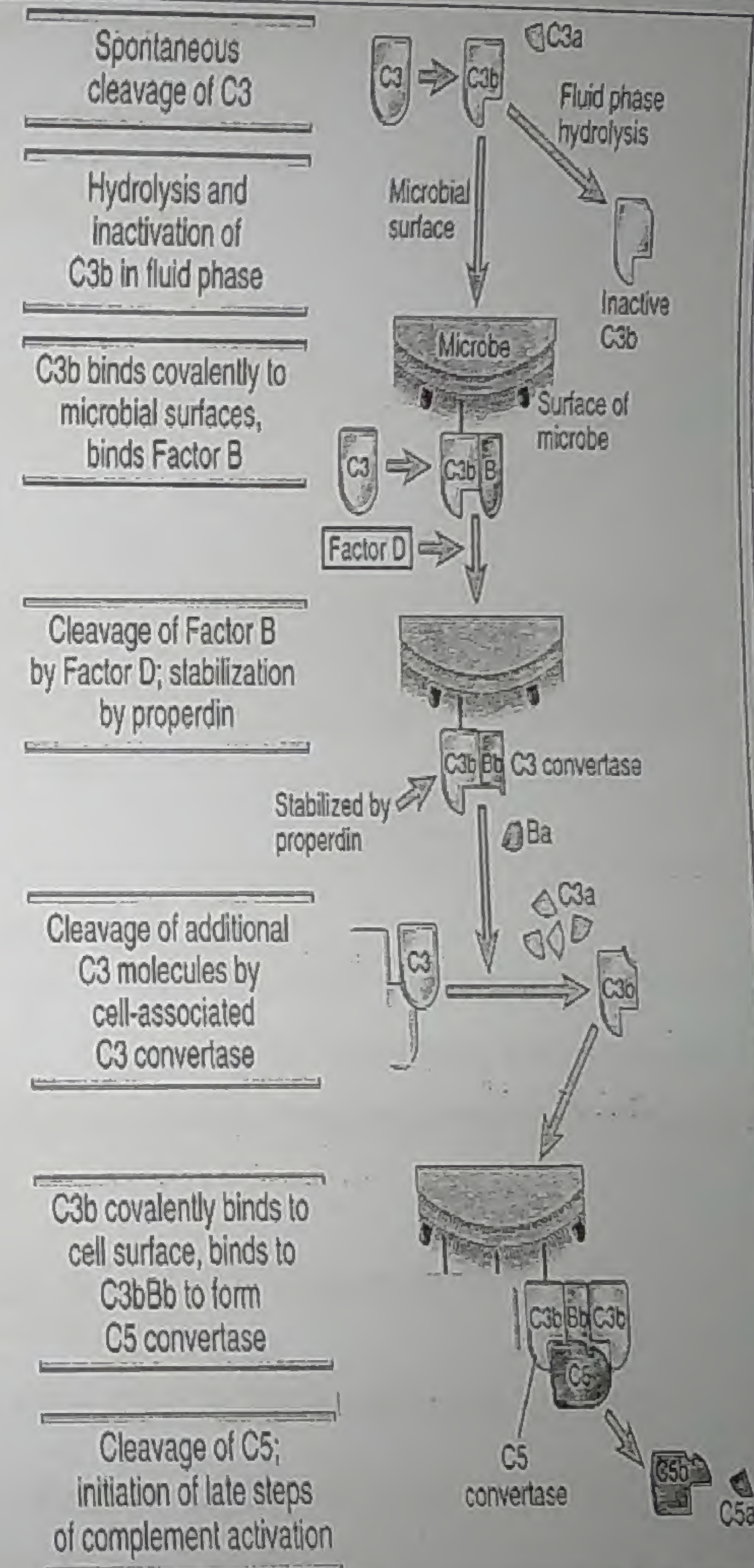
**C3b**

**Released** into  
surrounding space

**Reacts** with C3bBb

**C3bBb3b (C5 convertase)**

24





#### 4-Formation

of MAC  
Membrane attack complex.  
(common  
final pathway)

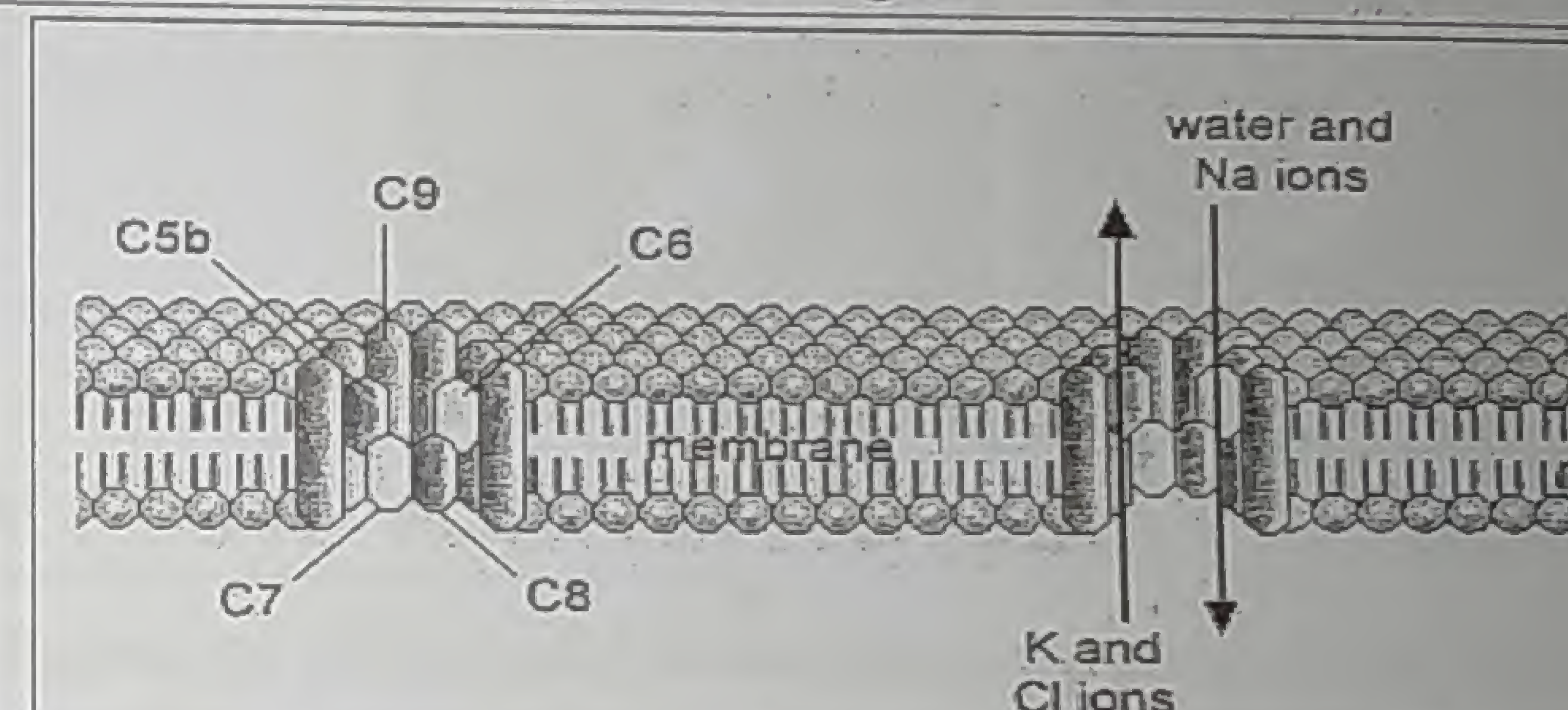
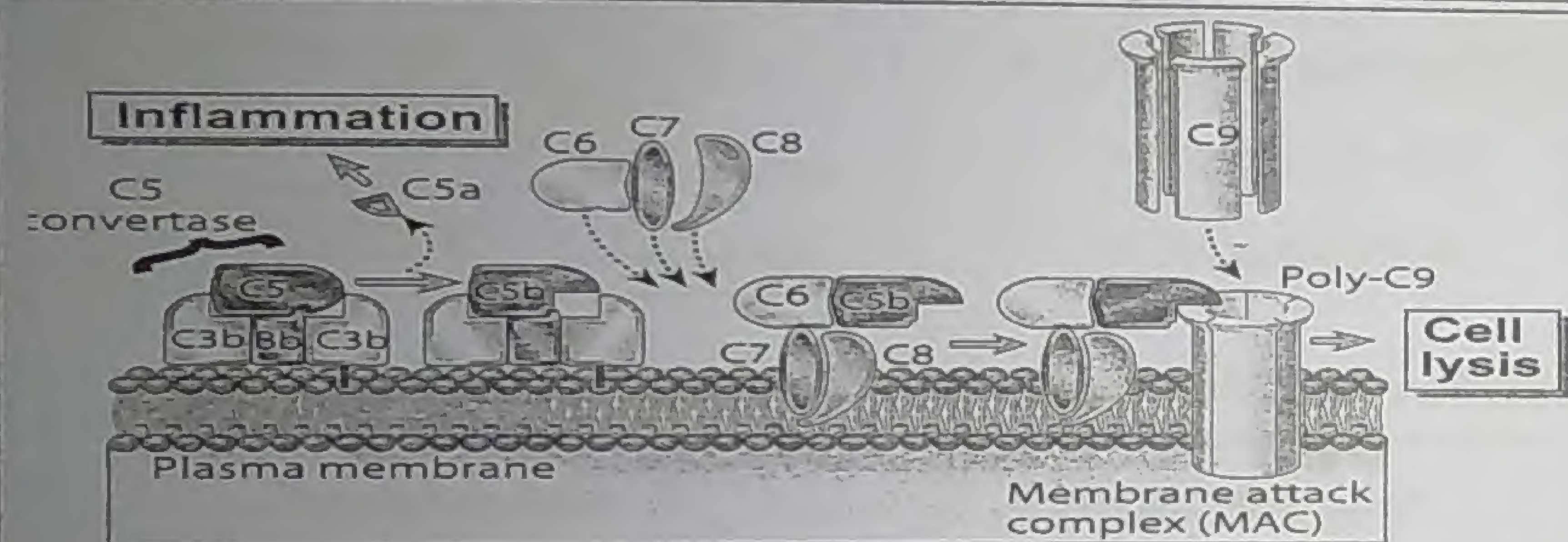
C5 convertase bind & cleave C5 into C5a (released into surrounding space) & C5b

C5b binds C6,7,8 & multiple mol. of C9 (C9 polymerized)

C5b6789 : Membrane attack complex (MAC)

Pores in target membrane

↑ IC Na → entry of water → osmotic swelling → Lysis of target



### Biological effects of complement

Cytolysis

Stimul. of inflam. response

Opsonization

↑ Ab production

Removal of immune complexes

#### 1- Cytolysis : by C5b6789 (MAC)

Insertion of MAC into CM → lysis of many cells : bacteria, viruses, fungi, parasites, VICs & tumor cells

MAC is more critical in lysis of bacteria with

thin CW (more vulnerable) e.g. *Neisseria* → deficiency in C5-8 leads to recurrent infection due to

MAC is less effective in lysis of bacteria with

thick CW & capsule e.g. *Strept. pneumoniae*



## II-Stimulation of inflammatory response

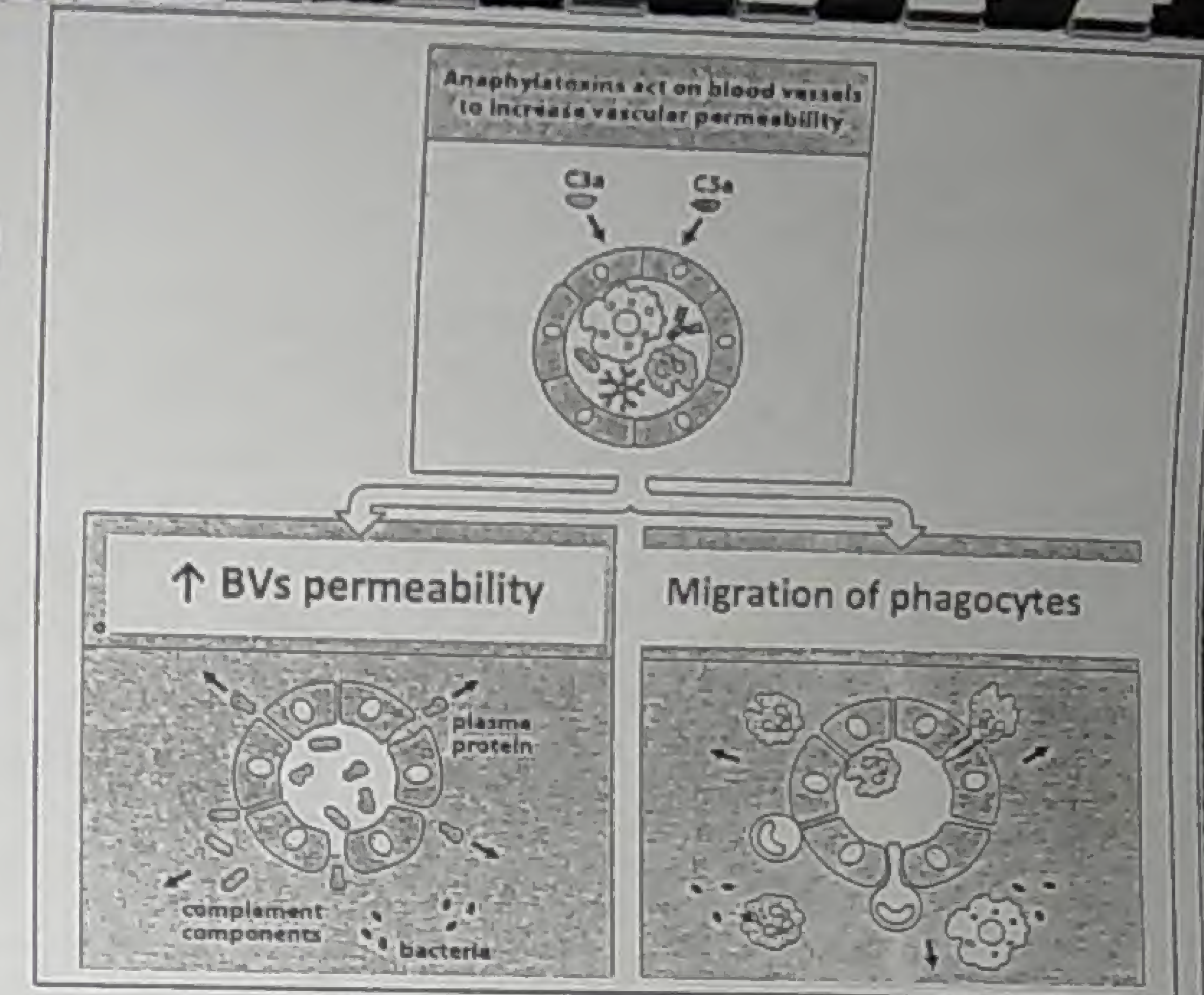
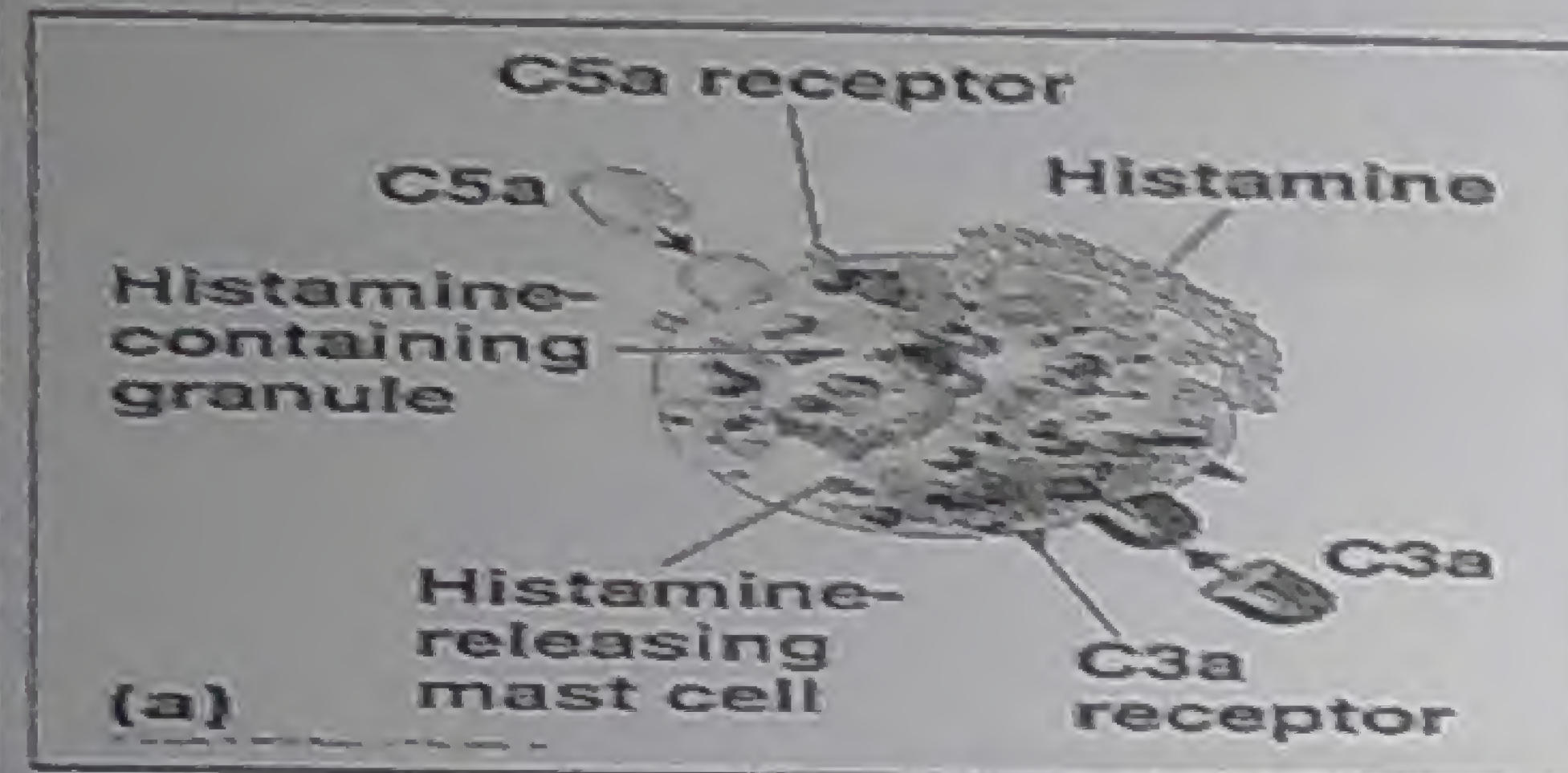
Chemotaxis : by C5a  
Attracts phagocytes  
to site of infection

Anaphylaxis : by anaphylatoxins (C3a, 4a & 5a)  
Attach to their receptors on mast cells

Degranulation & histamine release

Symptoms of anaphylaxis:

- ◆ ↑ vascular permeability
- ◆ Sm contraction
- ◆ Bronchospasm



## III- Opsonization, ↑ Ab production & removal of ICs : by C3b

Opsonization

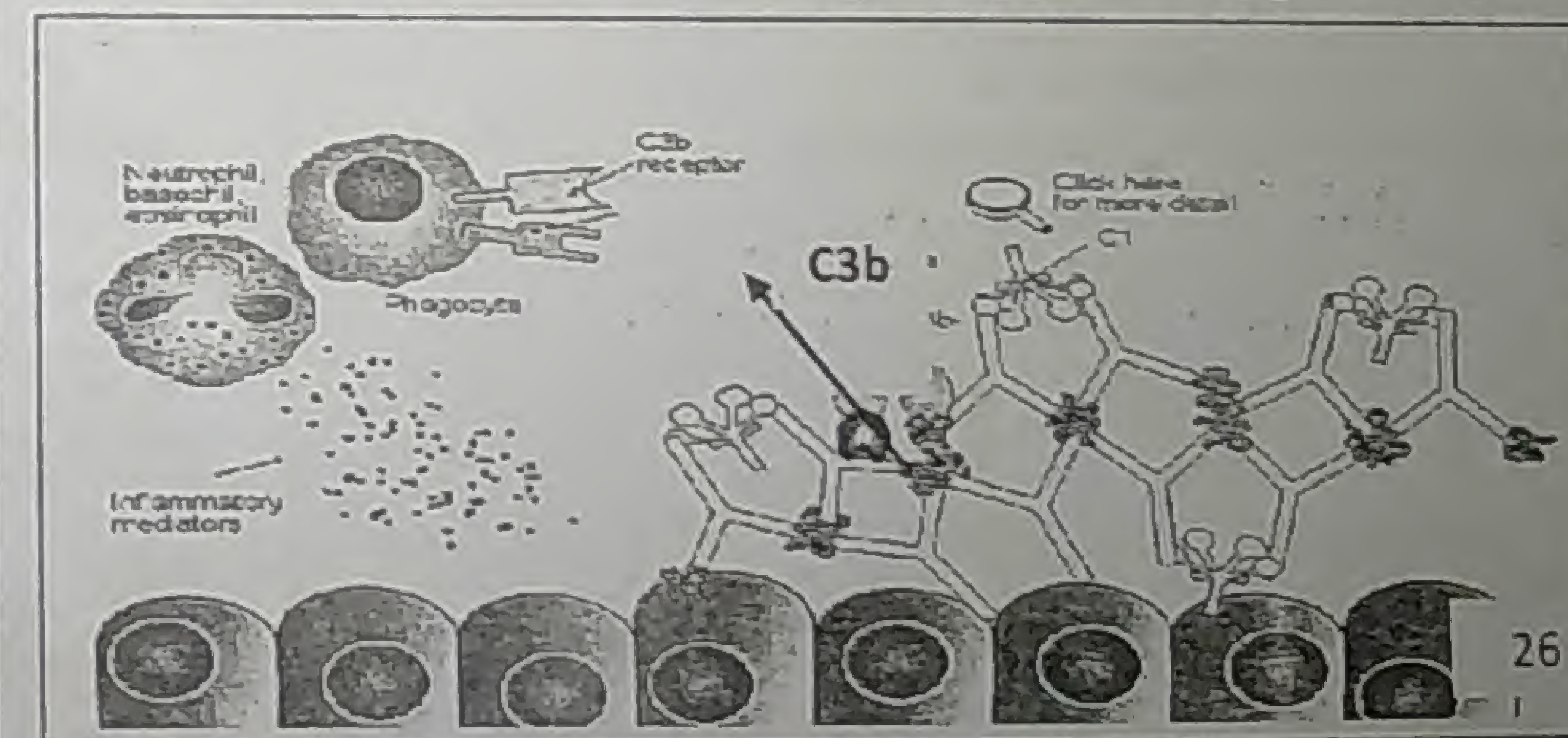
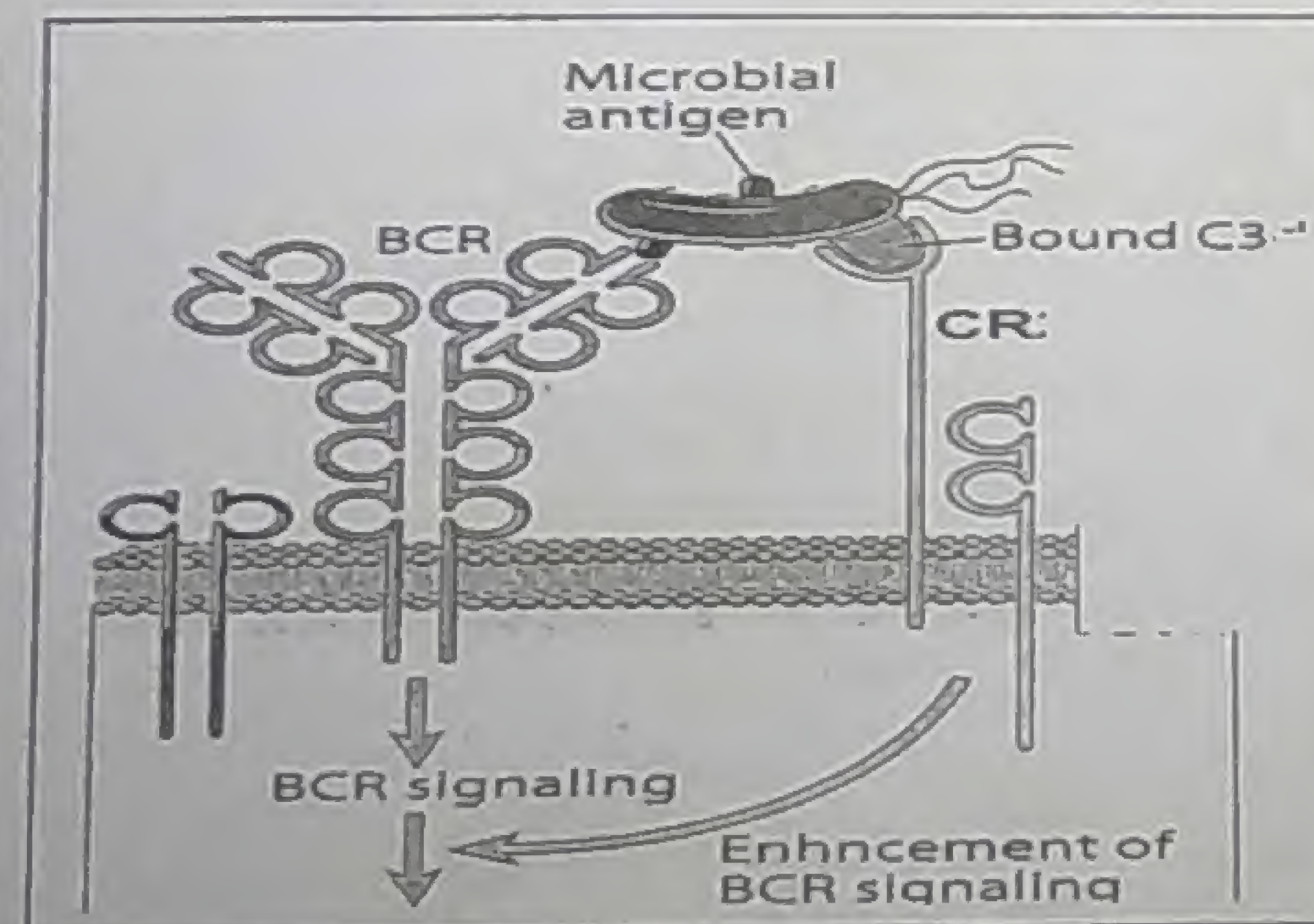
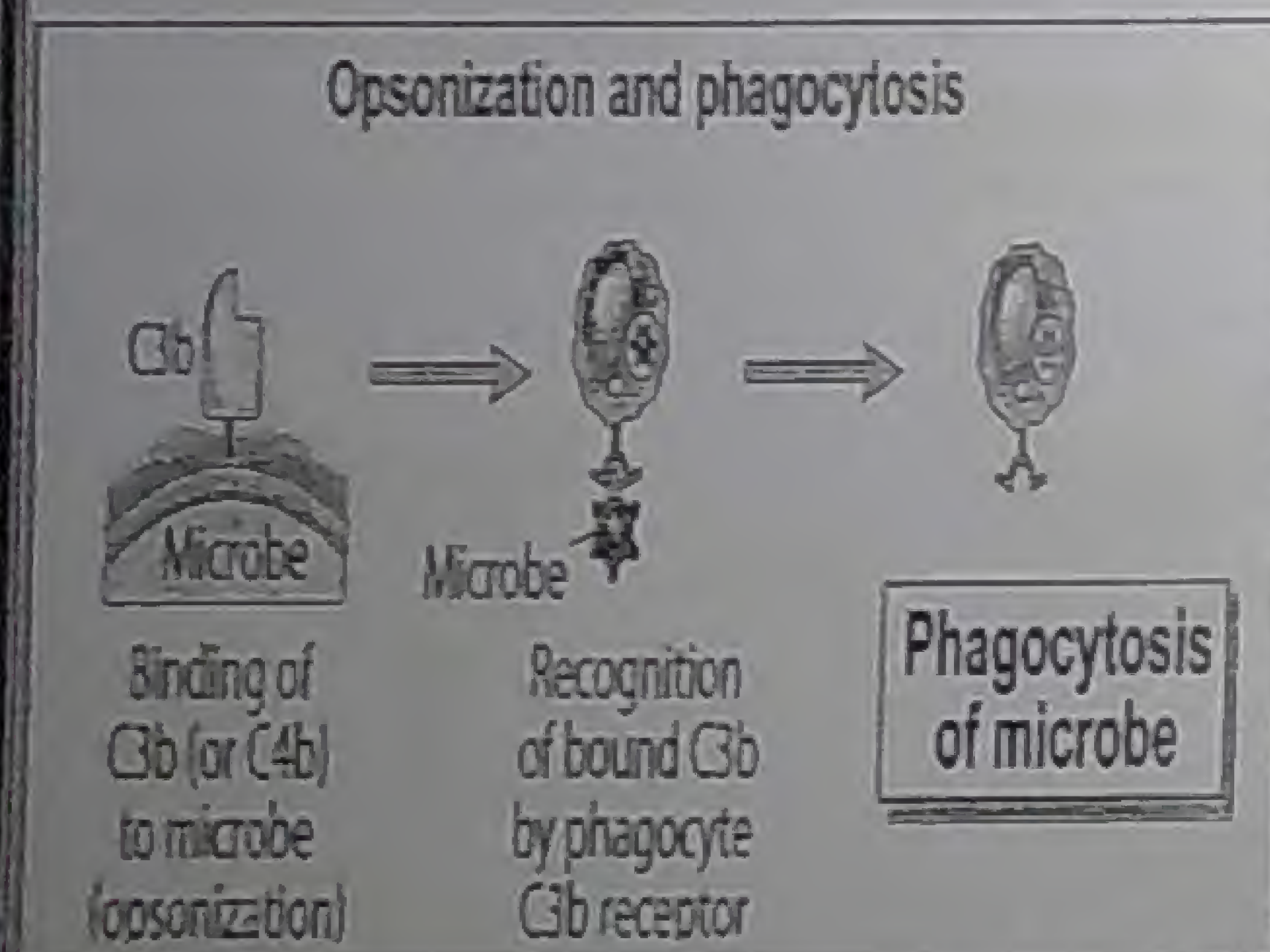
C3b coats bacteria & viruses  
Binds to C3bR on phagocytes  
Facilitates phagocytosis

↑ Ab production

C3b binds to  
C3bR on activated B cells  
↑ Ab production

Removal of harmful immunocomplexes from body

C3b deposits on ICs surface  
Facilitate their clearance from circulation by phagocyte  
Prevent their deposition in BVs wall  
Prevention of tissue damage (Type III hypersen.)





# Regulation of complement activation

## I-Proteins on surface of self cells

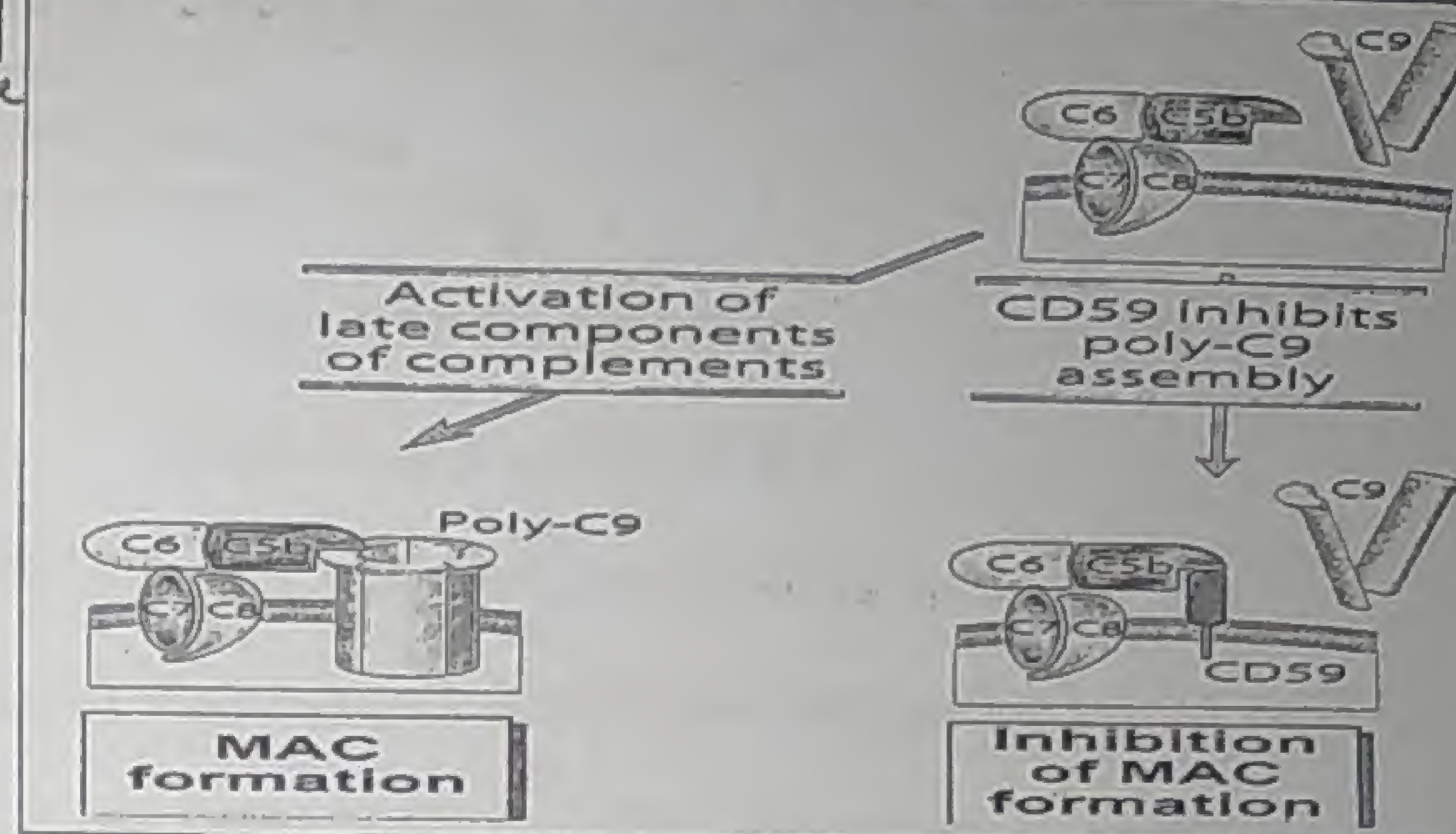
→ to avoid autoimmune diseases -

↑↑ levels of sialic acid  
on mammalian cells

Rapid inactivation of bound C3b  
on host cells

CD59 (Protectin)

⊖ C9 polymerization  
during formation of MAC



## II-Serum proteins → to avoid excess activation of complements

C1 inhibitor

Binds C1

⊖ activation of  
classical pathway

Decay acceleration factor (DAF)

Displaces

C2b from C4b

Bb from C3b

Dissociation of C3 convertase

Factor I

Cleaves C3b

Inactive C3b  
(iC3b)

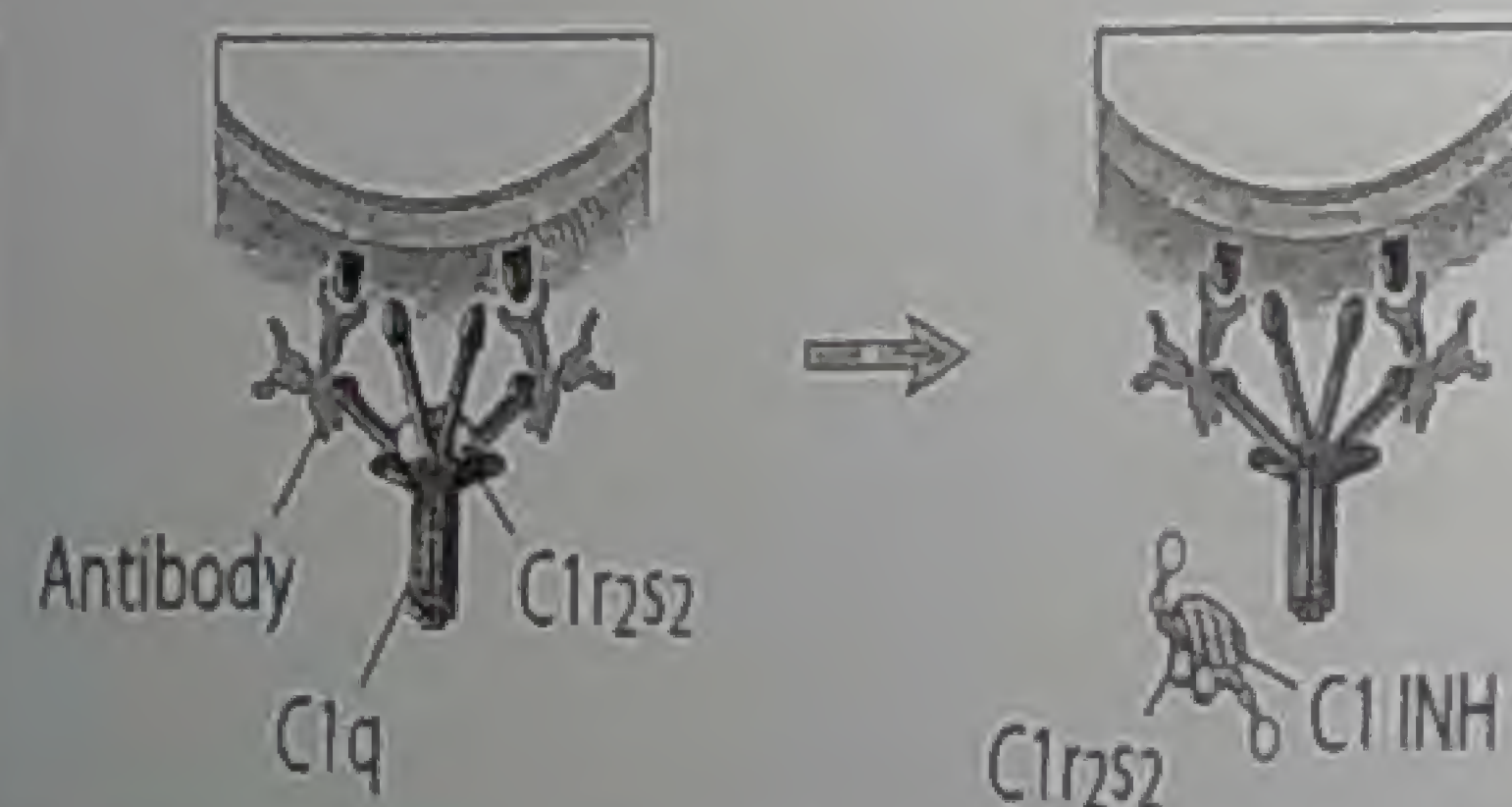
Factor H

Cofactor

in Factor I  
action

C1q binds to antigen-complexed antibodies, resulting in activation of C1r2s2

C1 INH prevents C1r2s2 from becoming proteolytically active



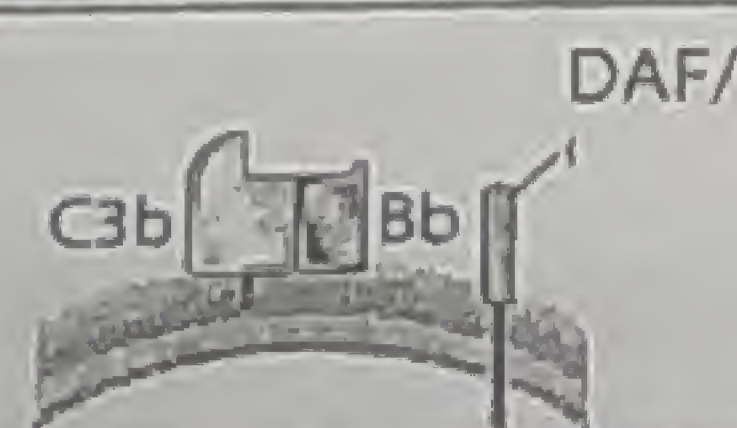
Formation of C4b2b complex (classical pathway C3 convertase)



DAF, displace C2b from C4b



Formation of C3bBb complex (alternative pathway C3 convertase)

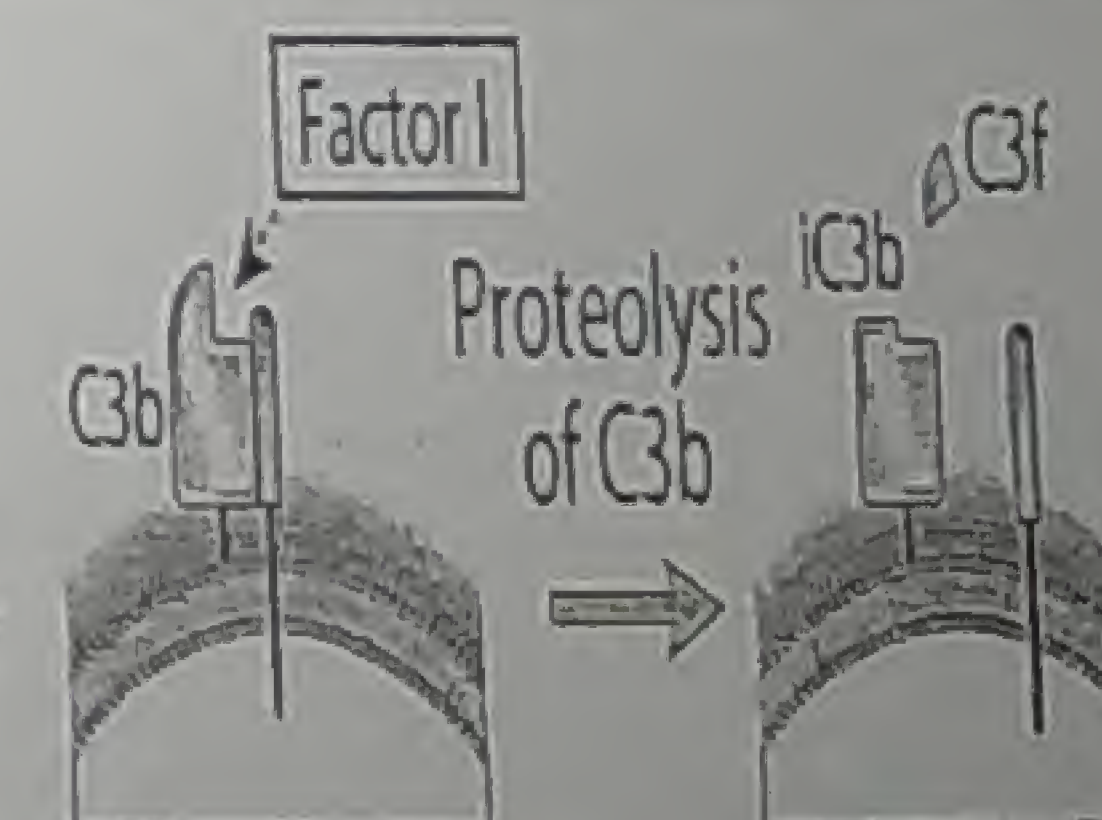


DAF, displace Bb from C3b



Factor I-mediated proteolytic cleavage of C3b, producing iC3b

27





## Clinical aspects of complement

### I-Deficiency of complement components

Recurrent acute (pyogenic)  
bacterial infections

*C3 deficiency is the most serious*

Loss of biological functions of complement:

- i. Lysis by MAC.
- ii. Opsonization. *→ recurrent infection with stript pneumoni*
- iii.  $\uparrow$  Ab production (  $\oplus$  of B cells)

Hypersensitivity

*Deficiency of C1, 4 & 2*

Defect in complement activation (C3)

Failure to remove ICs from circulation

Deposition of ICs in BVs & tissues

Inflammation & tissue damage

*→ Type III hypersensitivity & SLE*  
*Systemic lobus embolus*

### II-Inherited deficiency of C1 inhibitor ( C1 INH)

Hereditary angioneurotic edema

$\uparrow$  break down (  $\oplus$  ) of C4 & 2  
(  $\downarrow$  serum free level of C1, 2 & 4 )  
*not activated*

$\uparrow$  C3a, 4a & 5a  
(anaphylatoxins)

$\uparrow$  vasoactive amines

$\uparrow$  capillary permeability & localised edema at mucosal surface

Laryngeal edema

Airway obstruction

$\uparrow$  susceptibility to infections  
( *latent* )

Chronic consumption of C2 & C4

$\downarrow$  C3

### III - Autoimmune diseases

Bound Abs against cell surface proteins activate complement  $\rightarrow$  Cell lysis

### IV - Role in hyperacute graft rejection



# Immunogens & Antigens

## Immunogenecity

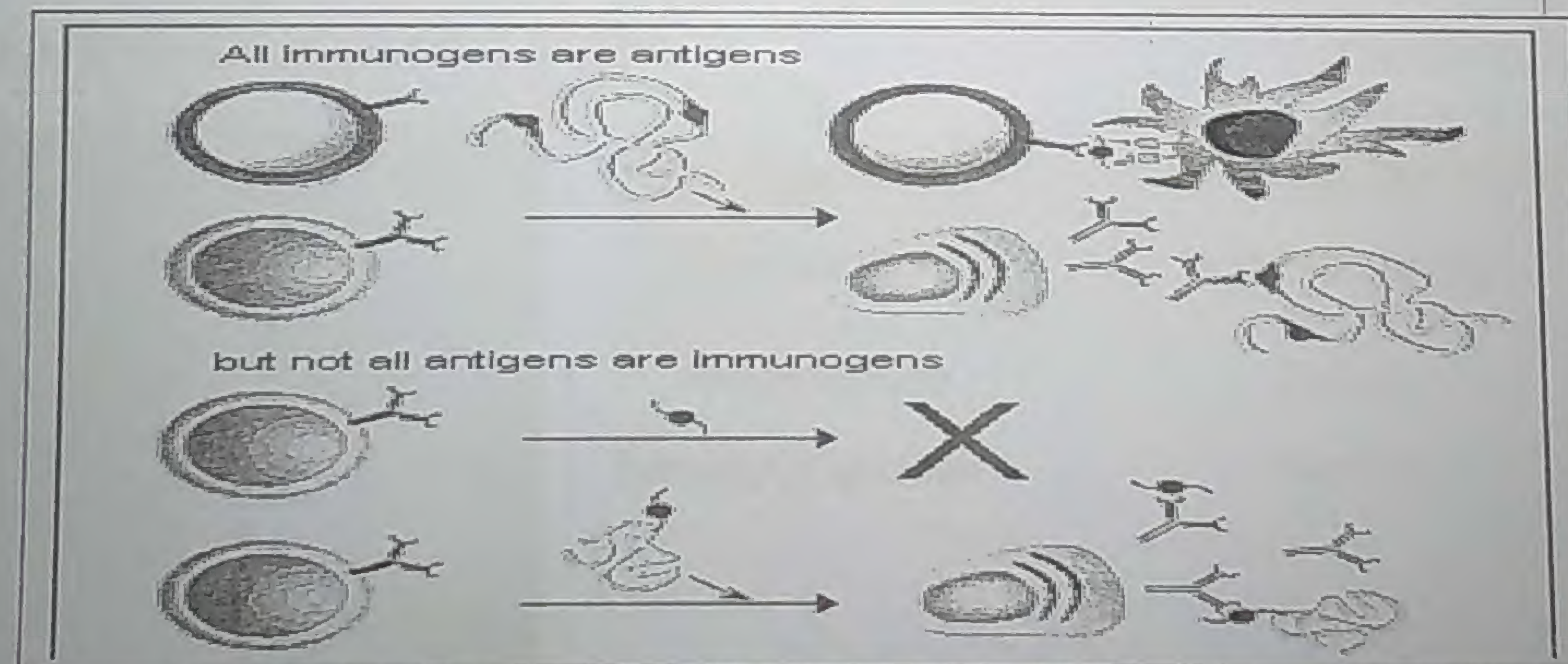
Is the ability of a substance (*Immunogen*) to induce a specific immune response

↓  
Production of Abs or activated T lymphocytes

## Antigenecity

Is the ability of a substance (Ag) to react (bind) specifically  
with *final products of IR* (Abs or activated T lymphocytes)

*All Immunogens are Ags, but not all Ags are immunogens*





# Haptens

## A-Characters

Not immunogenic

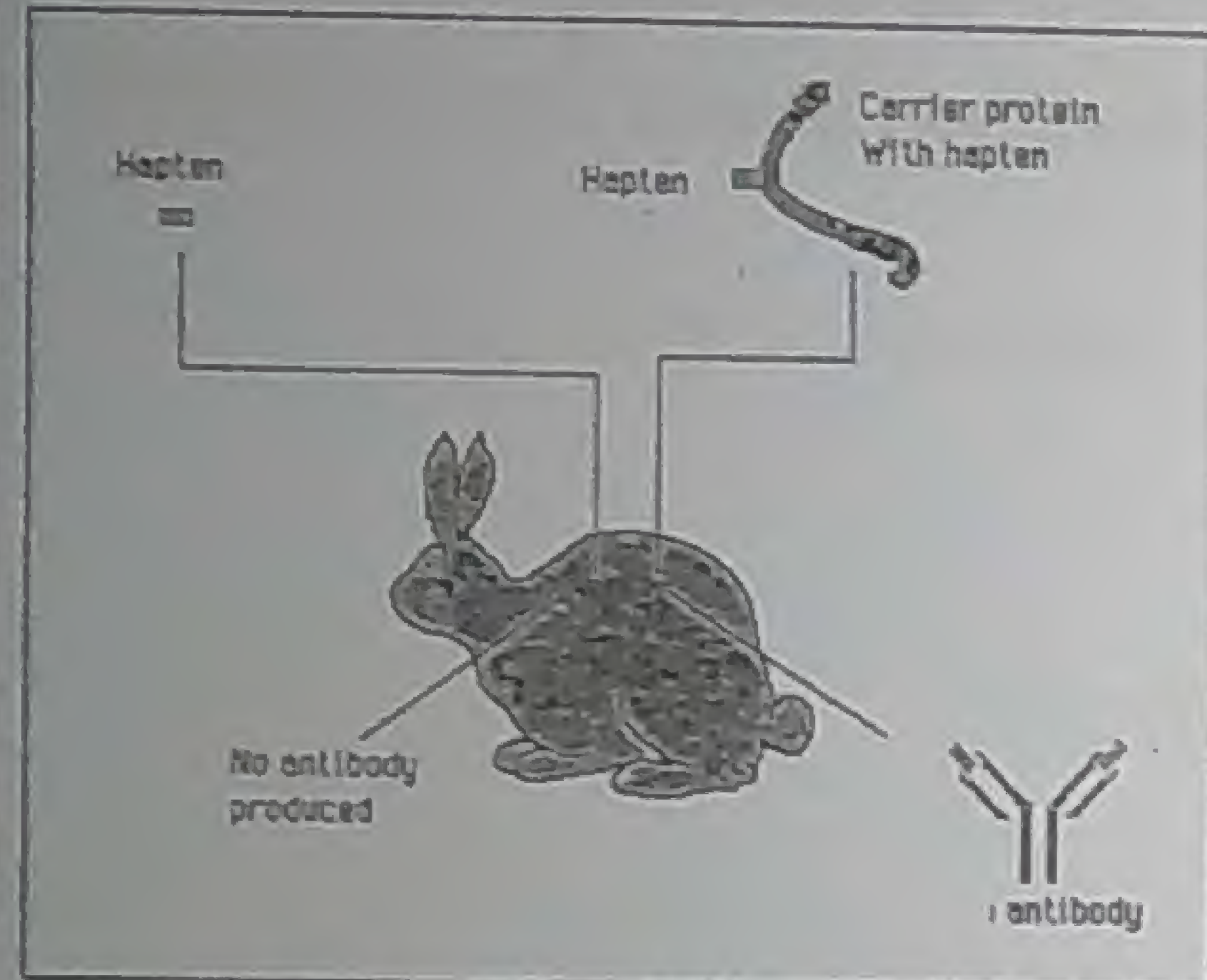
Due to its small MW

Becomes immunogenic

if conjugated to carrier proteins

Antigenic

React (bind)  
specifically with Abs



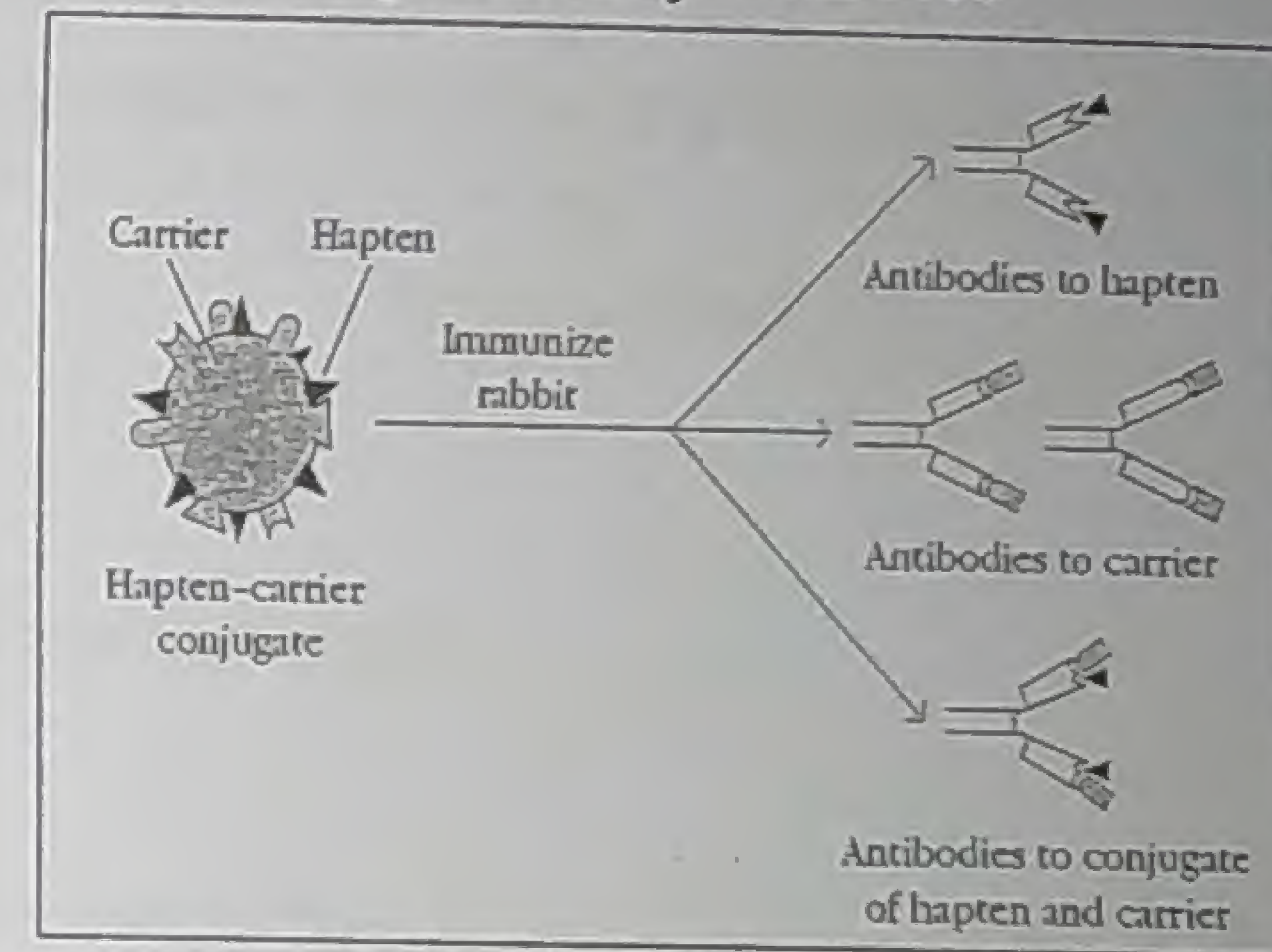
Hapten carrier complex (Immunogen)

⊕ B cells → Ab production against both

B-Examples & medical importance

Haptens can induce drug allergy

Penicillin

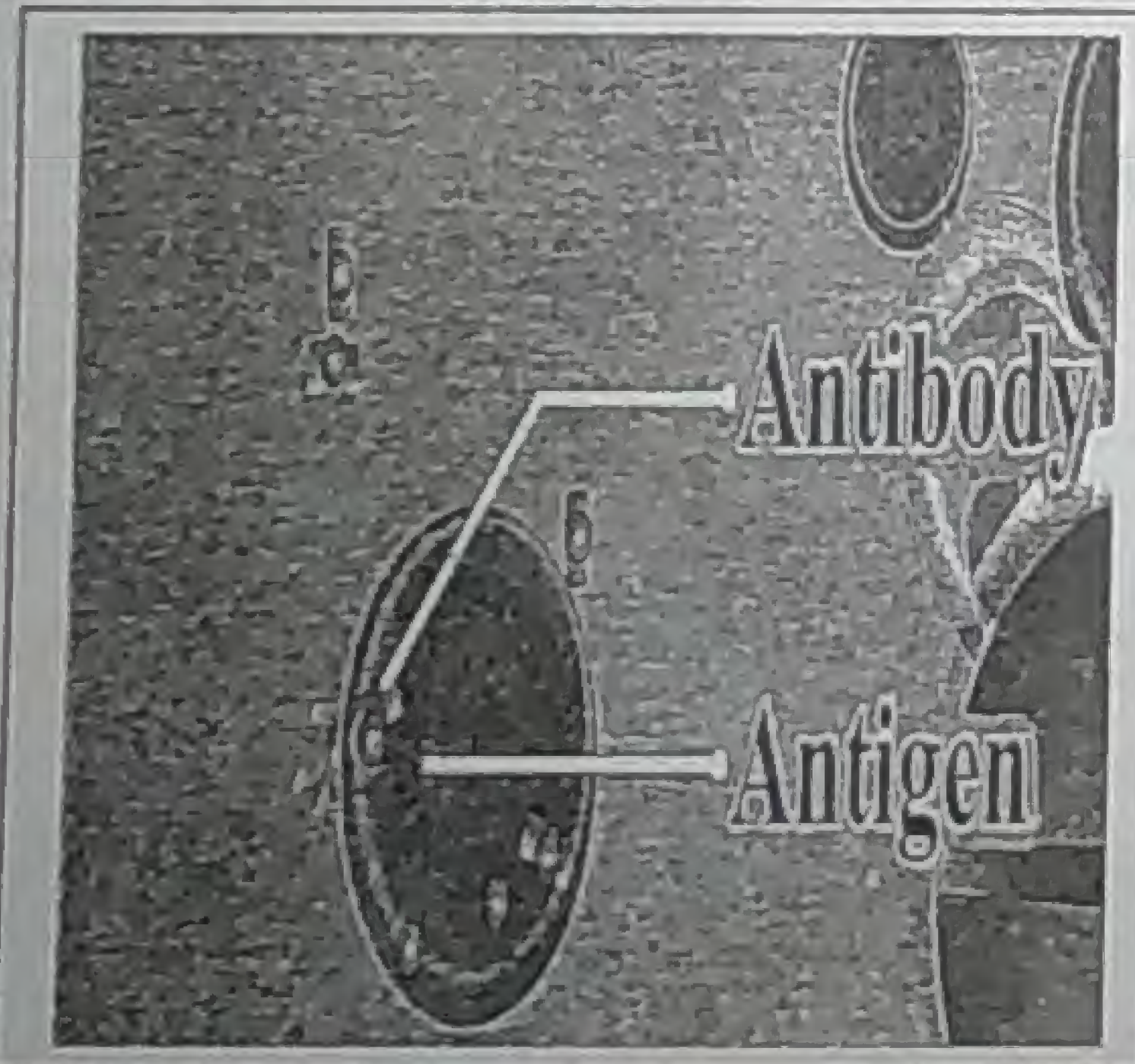


If binds to serum proteins or RBCs

Type I

hypersensitivity

Anaphylactic  
shock



Type II

hypersensitivity

Autoimmune  
hemolytic anemia

If binds to skin proteins

Type III

hypersensitivity

Arthus  
reaction

Type IV

hypersensitivity

Contact  
dermatitis



# Factors influencing immunogenicity

## 1-Foreignness

We are tolerant to self molecules → Only foreign Ags are immunogenic

## 2-Chemical composition

Proteins are more immunogenic  
than polysaccharides

Lipids & nucleic acids aren't immunogenic unless complexed with

↓      ↓

Proteins      Polysaccharides

## 3-Molecular size

The *higher* the molecular size → the *more potent* the immunogen

## 4-Dosage

Below a certain dose  
↓  
No ⊕ of immunity

Very high dose  
↓  
Immune paralysis

## 5-Route of administration

Ags injected SC, IM & ID induce the **strongest response**

Ags injected IV induce **weaker response**

↓  
Slow rate of absorption

↓  
Carried directly to LNs

↓  
Lack depot effect

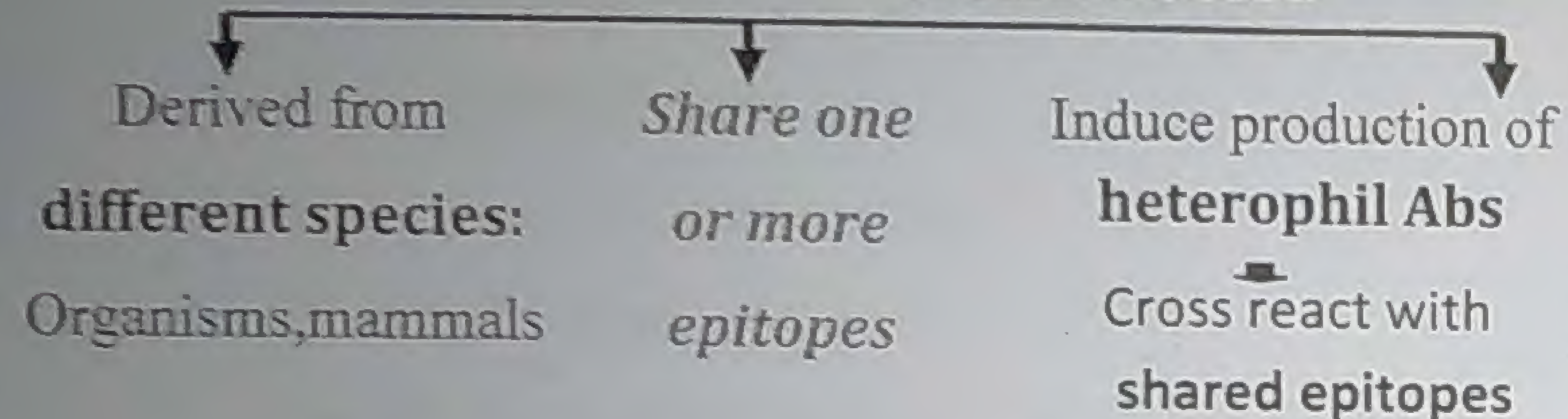
(depot effect)

↓  
Processed to ⊕ immune cells



# Heterophil Ags ( cross reactivity)

## I-Characters



## Practical Applications

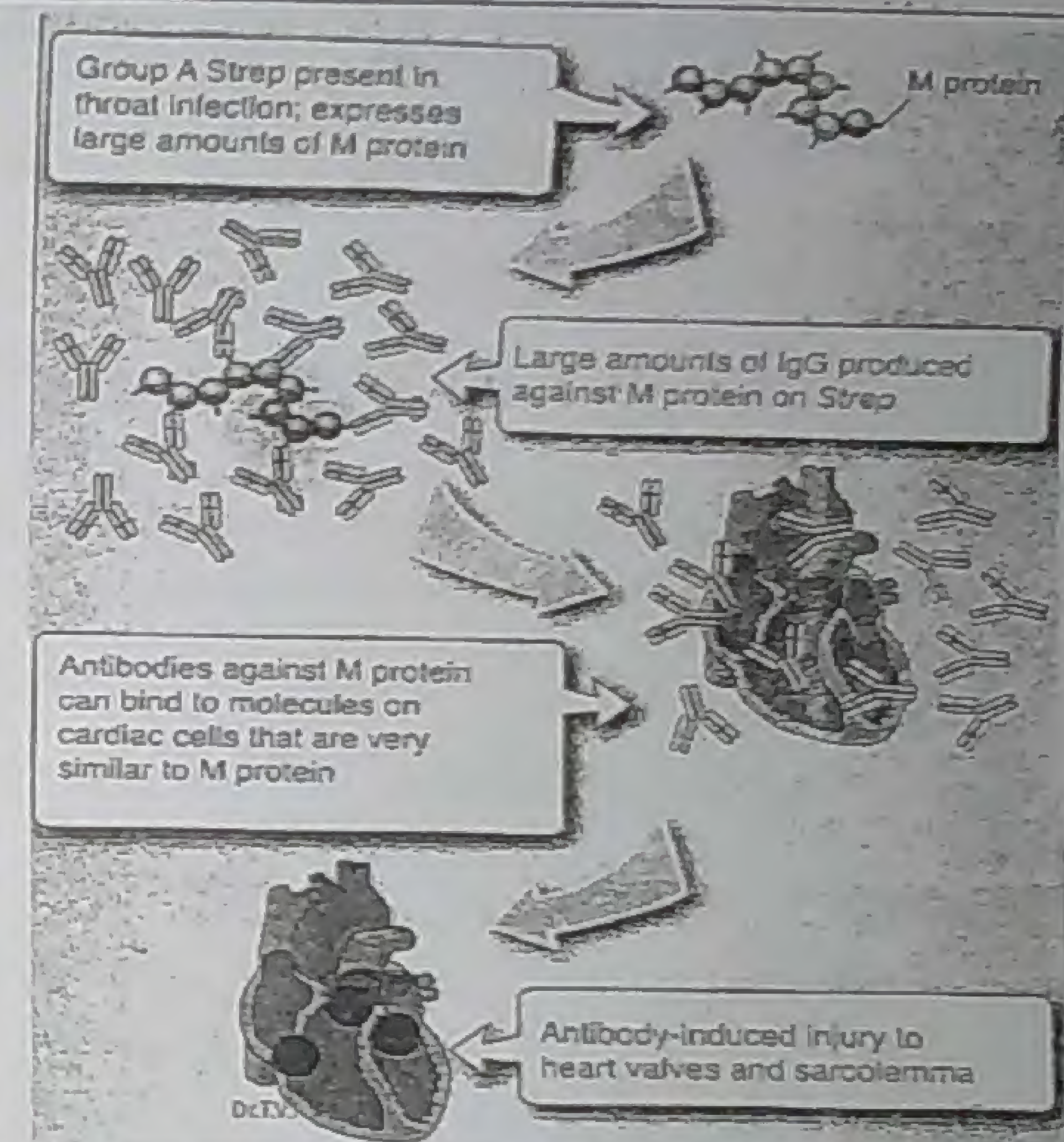
### A-Pathogenesis of Rheumatic Fever

Heterophil Abs produced against group A Streptococcus M protein

Cross react with *heart protein myosin*

### B-Laboratory diagnosis

Rheumatic fever is a classic example of molecular mimicry



Heterophil Abs in serum of patients cross react with added heterophil Ags → diagnosis of many diseases

Disease	Causative organism	Used heterophil Ag	Test
1-Syphilis	Treponema pallidum	Cardiolipin (beef heart muscle + cholesterol + lecithin)	Wassermann test
2-Typhus fever	Rickettsia	Non motile strains of proteus (OX19, OX2 & OXK)	Weil Felix test
3-Infectious mononucleosis	Epstein-Barr virus	Sheep RBCs 32	Paul Bunnell test



# Monoclonal Abs

## Definition

Mc Ab is an Ab produced by  
a single clone of B cell  
*Specific for a single epitope*

## Method of production

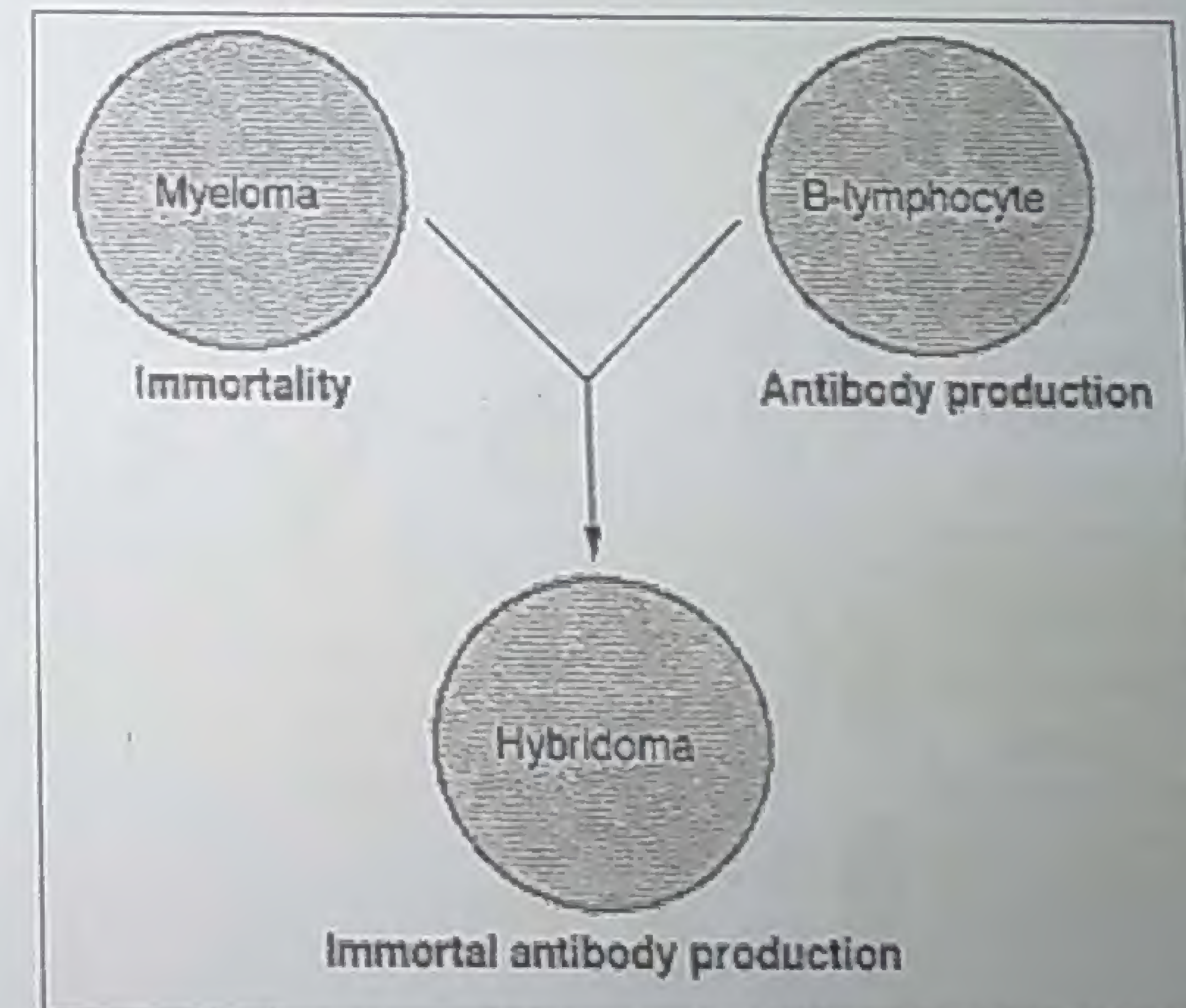
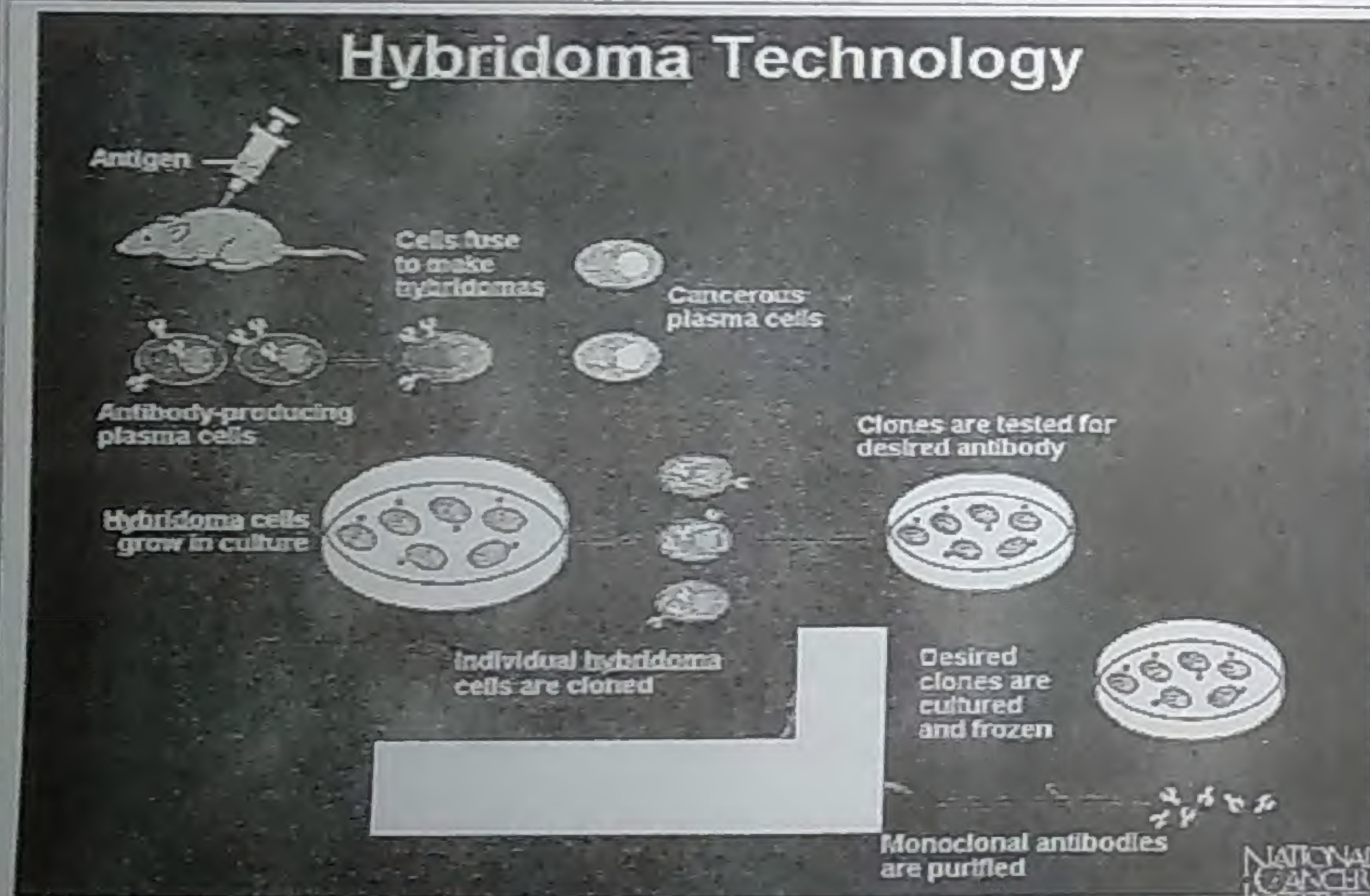
B cells producing the **desired single kind Ab**  
are fused with **tumor cells** (myeloma cells)

Production of *hybridoma cells*

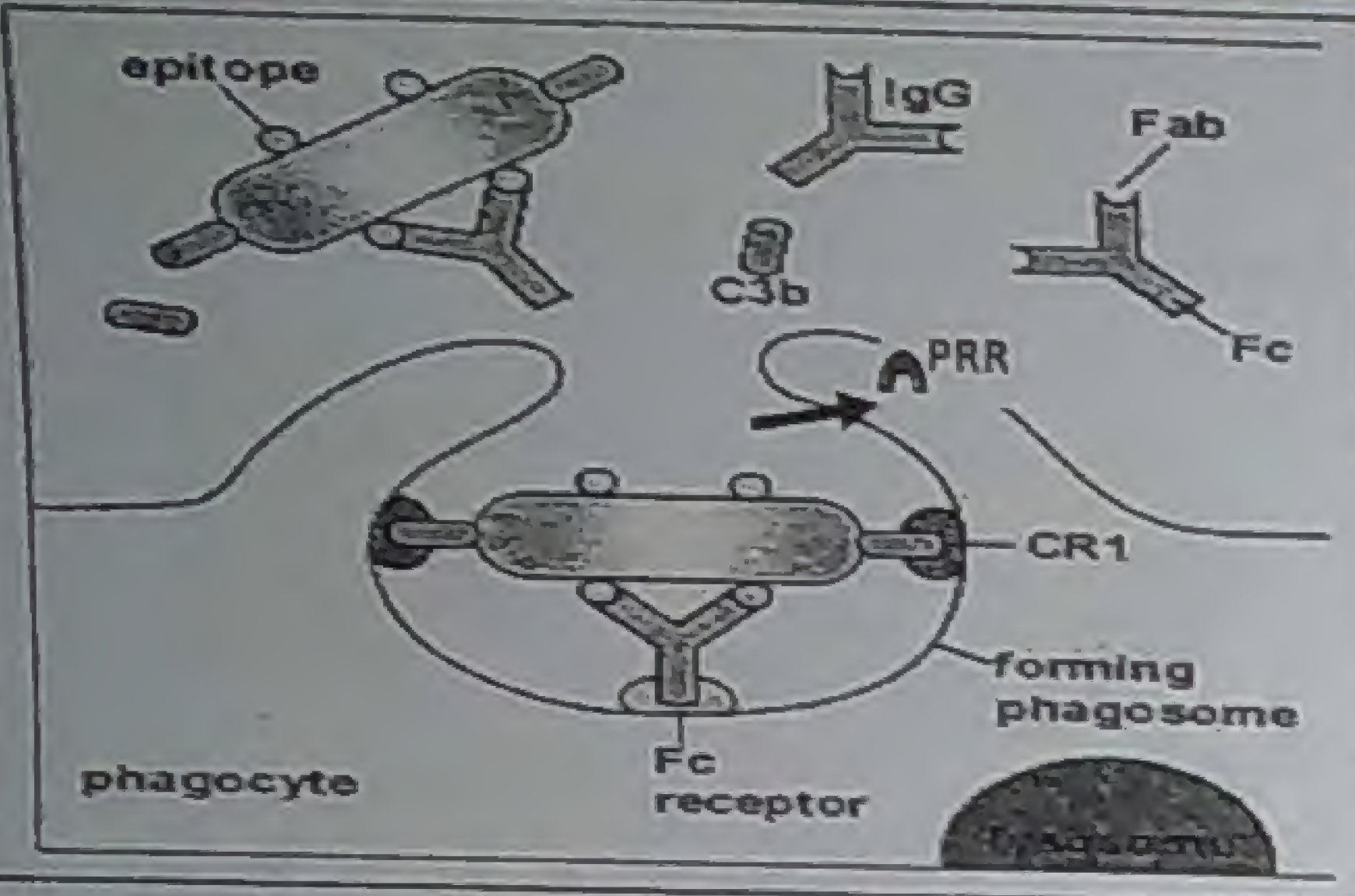
Secrete the  
desired Mc Ab

Long lived  
(indefinite multiplication)

## Hybridoma Technology







# Immunity against microbes

## Immunity against EC bacteria

### I-Innate immunity

#### Phagocytosis

Phagocytes bind ECB by

PRRs & opsonin receptors : C3bR & IgGR

Ingested bacteria are killed & digested

by lysosomes

Activated MQ secrete

inflammatory cytokines

Recruitment of leukocytes

to sites of inf.

#### Complement activation

ECB activate

alternative or lectin pathways

Bacterial lysis, opsonization &

enhancement of inflammation

### II-Adaptive immunity

Humoral immunity : the main protective IR

Neutralization Opsonization Complement activation

By classical pathway

### III-Mechanisms of evasion of IR

Antigenic variation  
of surface Ag

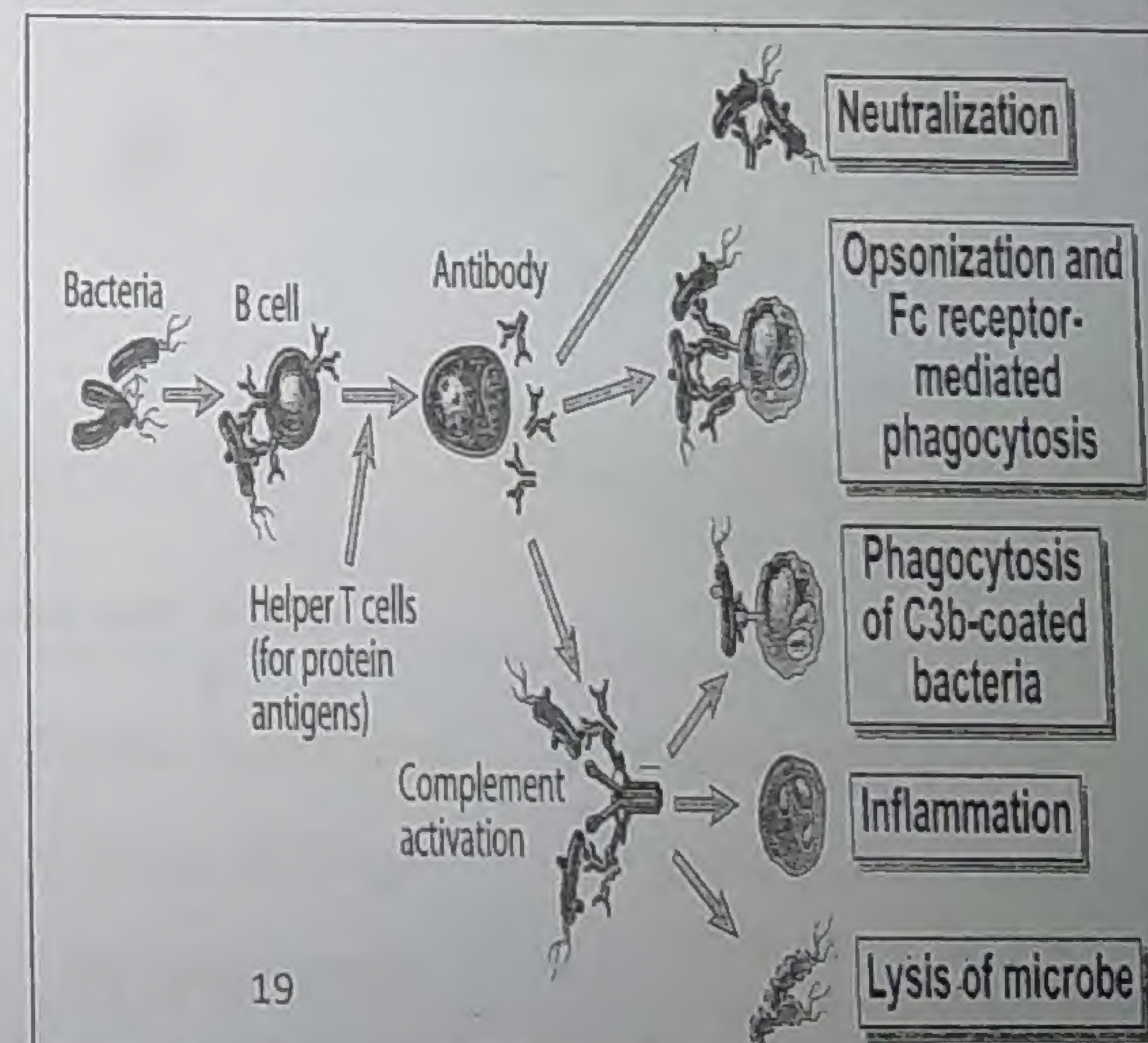
during replication in host

e.g Salmonella & Borrelia

Polysaccharide capsule :  
antiphagocytic

Sialic acid in capsulated G<sup>+</sup>ve & -ve bact.

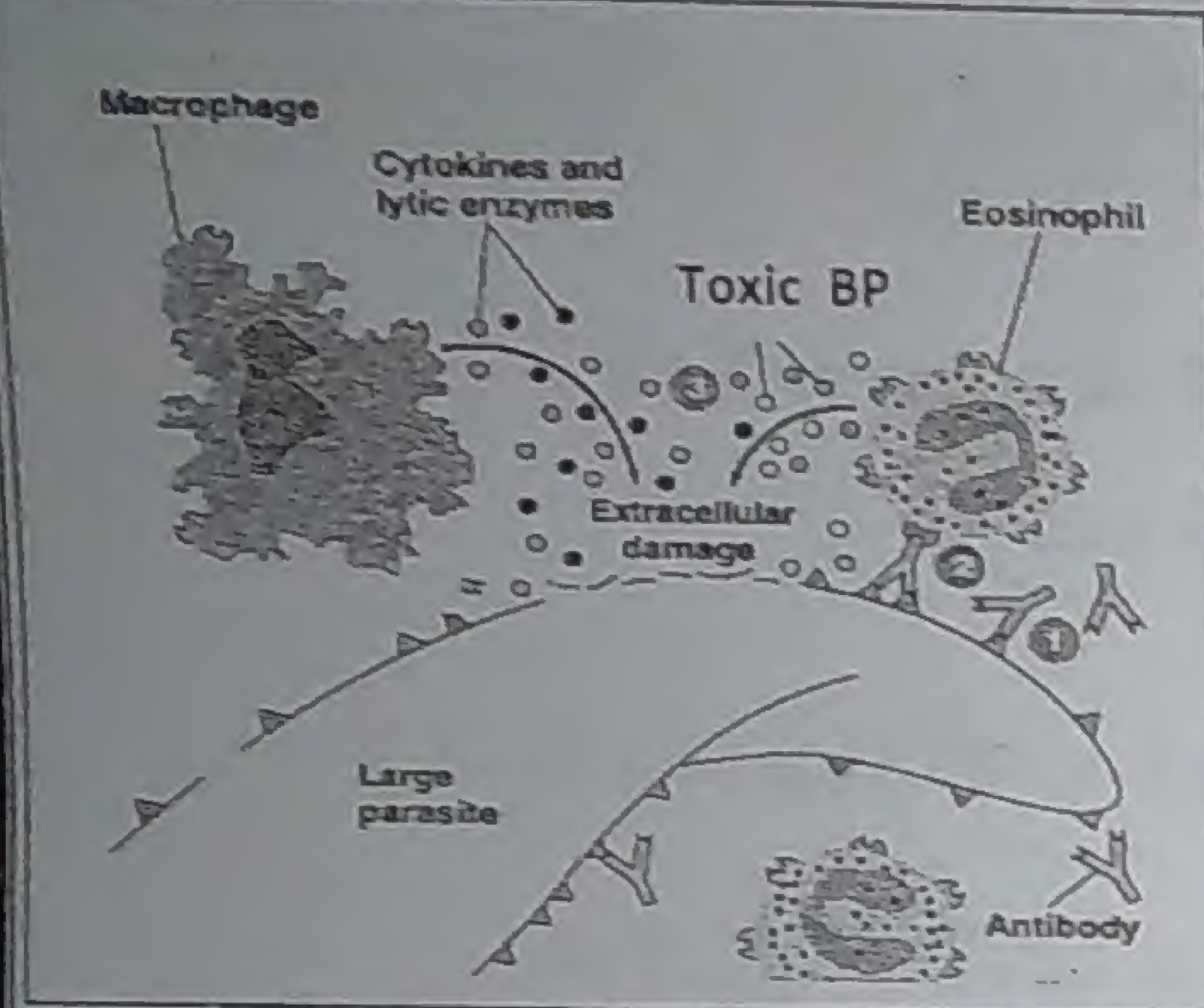
⊖ complement activation by alternative path.





# Immunity against parasites

## I-Innate immunity



### Phagocytosis

Although it is the main mechanism, many parasites resist killing

Replicate within MQ

Phagocytes release their granular contents

Kill *too big* parasites to be phagocytosed

### Complement activation

Parasites activate *alternative* pathway

## II-Adaptive immunity

**Humoral immunity** : the main protective IR

### ADCC

Th2 secrete IL4&5

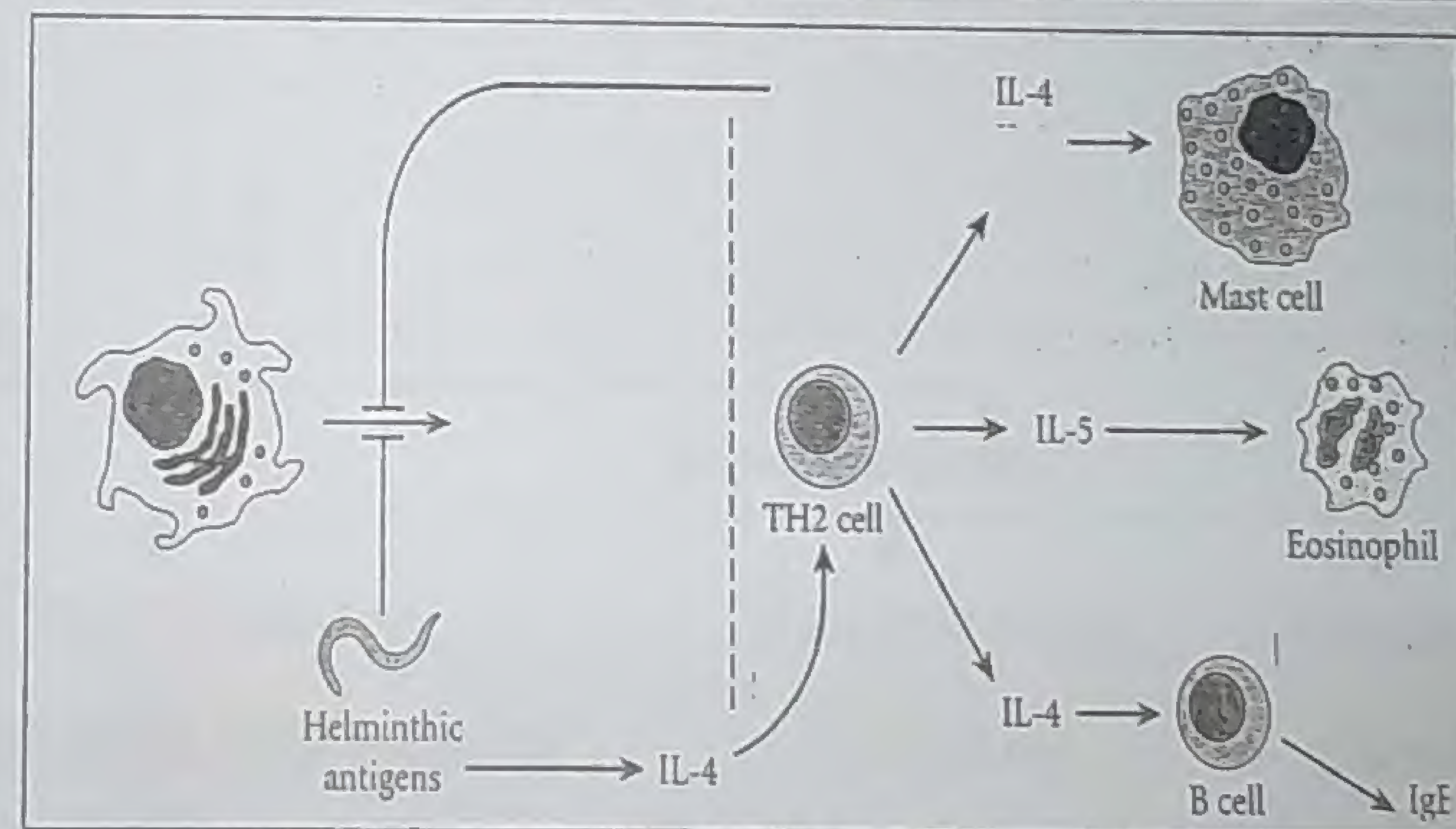
↑ IgE & ⊕ eosinophils

IgE coating parasites bind to Fcε R on eosinophils

Degranulation

*Release of toxic basic protein*

Killing parasites by ADCC



CMI

CTLs kill

parasites

replicating

in host cells

## III-Mechanisms of evasion of IR

Antigenic variation

of surface Ag during replication in host cell

Immunosuppression

⊕ of T reg

Production of IS cytokines

Thick tegument

Resist killing by lysosomes

Developing cysts

*Concealing* from immune effector mechanisms



# Immunity against viruses

## I-Innate immunity

See before

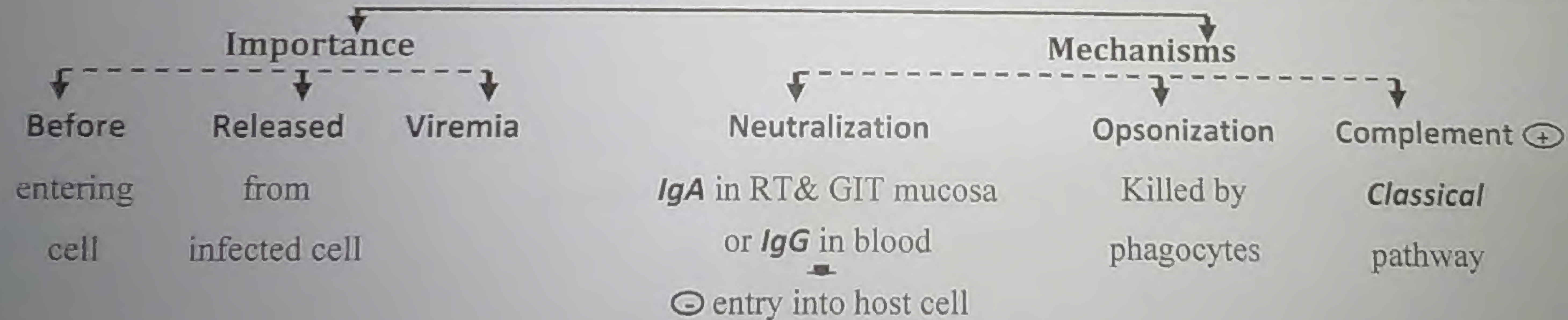
## II-Adaptive immunity

### A-CMI : The main immunity

See before

### B-Humoral immunity

#### 1-Killing viruses



#### 2-Killing VIC

